Table 10-7 Study specific details and $PM_{2.5}$ concentrations from recent studies that examined cancer survival.

Study Location, Years, Data	Population/Cancer	Mean Concentration µg/m^3	Exposure Assessment	Results
†Xu et al. (2013) Los Angeles, CA; Honolulu, HI 1992–2008 SEER	58,586 respiratory cancer cases among whites LA: 56,193 Honolulu: 2,393	LA: 18.1 Honolulu: 4.3	Average of all monitors in the county where the case resided to calculate county-level monthly mean, each case assigned monthly mean concentration for each month after diagnosis.	Kaplan-Meier Survival Analysis: Higher mortality rate for respiratory cancer cases in areas with high $PM_{2.5}$ concentrations (LA) vs. low (Honolulu) Cox Proportional Hazards Model: Categorical analysis (LA only):[a] Overall mortality: HR = 1.07 (95% CI: 1.02, 1.13) Respiratory cancer mortality: HR = 1.08 (1.02, 1.14) Continuous variable analysis (per 5 µg/m^3): Overall mortality: HR = 1.57 (95% CI: 1.53, 1.61) Respiratory cancer mortality: HR = 1.49 (1.45, 1.53)

Table 10-7 (Continued): Study specific details and $PM_{2.5}$ concentrations from recent studies that examined cancer survival.

Study Location, Years, Data	Population/Cancer	Mean Concentration µg/m^3	Exposure Assessment	Results
†Eckel et al. (2016) 1988–2009[b] California CCR	352,053 lung cancer cases	13.7	Monthly average concentrations interpolated to residential address using IDW of up to four closest monitors within 50 km radius; however, cases excluded if nearest monitor was >25 km away. Each case assigned monthly mean for each month after diagnosis.	Cox Proportional Hazards Model (per 5 µg/m^3): All-cause mortality: HR = 1.15 (95% CI: 1.15, 1.16) Lung cancer mortality: HR = 1.14 (95% CI: 1.13, 1.15)
†Hu et al. (2013) California 1999–2009 CA SEER	255,128 female breast cancer cases	—	Average of all monitors in the county where the case resided to calculate county-level monthly mean, each case assigned monthly mean concentration for each month after diagnosis. Cases excluded if any missing PM data during any month.	Kaplan-Meier Survival Analysis: Higher mortality rate for breast cancer cases living in counties with high $PM_{2.5}$ concentrations vs. low Cox Proportional Hazards Model: Breast cancer mortality: Categorical analysis:[d] 11.64–15.04 µg/m^3: 1.24 (95% CI: 0.79, 1.94) ≥15.04 µg/m^3: 1.76 (95% CI: 1.24, 2.49) Continuous analysis (per 5 µg/m^3): HR = 1.86 (95% CI: 1.12, 3.10)

Table 10-7 (Continued): Study specific details and $PM_{2.5}$ concentrations from recent studies that examined cancer survival.

Study Location, Years, Data	Population/Cancer	Mean Concentration µg/m^3	Exposure Assessment	Results
†Deng et al. (2017) California 2000–2009 CCR	22,221 HCC liver cancer patients	Total: 13.3 Local: 12.9 Regional: 13.3 Distant: 14.0	Same approach as described in Eckel et al. (2016) above.	Kaplan-Meier Survival Analysis: Median survival (years) was higher for all-cause mortality for liver cancer patients overall, and specifically for local and regional stage patients. Cox Proportional Hazards Model: Categorical Analysis:[e] Overall Results: 10–15 µg/m^3: 15–20 µg/m^3: 1.18 (95% CI: 1.12, 1.24) 20–25 µg/m^3: 1.46 (95% CI: 1.36, 1.57) 25–30 µg/m^3: 2.40 (95% CI: 2.14, 2.69) ≥30 µg/m^3: 4.61 (95% CI: 3.87, 5.50) Continuous Analysis (per 5 µg/m^3): 1.18 (95% CI: 1.16, 1.20)

CA SEER = California Surveillance Epidemiology and End Results cancer registry; CCR = California Cancer Registry; HHC = hepatocellular carcinoma; SEER = Surveillance Epidemiology and End Results cancer registry.

[a]Honolulu cases were the referent, for both categorical and continuous analysis results are for the fully adjusted model.

[b]For $PM_{2.5}$ analysis, only cases diagnosed in 1998 or later included.

[c]Mean $PM_{2.5}$ concentration not reported, but study conducted categorical analysis with $PM_{2.5}$ tertiles of <11.64 µg/m^3, 11.64–15.04 µg/m^3, and ≥15.04 µg/m^3.

[d]11.64 µg/m^3 was the referent, results are for the fully adjusted mode.

[e]<10 µg/m^3 was the referent.

†Studies published since the 2009 PM ISA.

Xu et al. (2013) and Eckel et al. (2016) examined cancer survival by focusing on both the influence of $PM_{2.5}$ concentrations on overall survival as well as the risk of death or cancer-related death in individuals with any respiratory cancer or lung cancer, respectively. Xu et al. (2013) focused on two areas representative of high (Los Angeles) and low (Honolulu) $PM_{2.5}$ concentrations, while Eckel et al. (2016) focused specifically on whether lung cancer cases resided in areas with higher and lower $PM_{2.5}$ concentrations. In Xu et al. (2013) and Eckel et al. (2016), cancer survival was found to decrease in areas with higher $PM_{2.5}$ concentrations, which was further supported by the categorical analysis conducted in Xu et al. (2013) where there was evidence of increased risk of mortality among people with cancer when comparing the higher polluted area (Los Angeles) with the lower polluted area (Honolulu). Additionally, in analyses in both studies where $PM_{2.5}$ was included as a continuous variable there was evidence of positive associations between long-term $PM_{2.5}$ exposure and overall mortality and respiratory/lung cancer mortality (Table 10-7).

Additional evidence indicating a potential relationship between cancer survival and long-term $PM_{2.5}$ concentrations was provided by studies conducted in California that examined breast cancer survival (Hu et al., 2013) and liver cancer survival (Deng et al., 2017). Hu et al. (2013) reported evidence of higher breast cancer mortality in cases living in counties with higher $PM_{2.5}$ concentrations as well as a high overall risk of breast cancer death. In the study of liver cancer survival, Deng et al. (2017) observed an overall increase in the risk of all-cause mortality as well as evidence that mortality risk increases in liver cancer patients as $PM_{2.5}$ concentrations increased (Table 10-7). Both of these studies provide initial evidence that although long-term $PM_{2.5}$ exposure has not been associated with breast cancer incidence, and only a few studies have examined liver cancer incidence (see Section 10.2.5.3), underlying cancer may contribute to increasing the risk of death after diagnosis.

In addition to examining overall cancer survival, Eckel et al. (2016), Hu et al. (2013), and Deng et al. (2017) examined whether the stage of cancer diagnosis modified survival. In each of these studies there was initial evidence, through categorical analyses, of a nonlinear relationship between $PM_{2.5}$ exposure and cancer survival, where patients with less advanced cancer at diagnosis (i.e., local or regional) had lower survival if they resided in locations with higher compared to lower $PM_{2.5}$ concentrations (Table 10-7). This pattern of associations was not observed in patients diagnosed with distant (i.e., late) stage cancer likely due to the advanced stage of cancer and overall lower survival rate. Collectively, these studies provide initial evidence that exposure to long-term $PM_{2.5}$ concentrations may contribute to reduced cancer survival. However, caution is warranted in the interpretation of the results from these studies because they are all conducted in one location, California.

10.2.6 Associations between $PM_{2.5}$ Sources and Components and Cancer

As characterized throughout this ISA, PM itself is a complex mixture consisting of numerous individual components derived from a variety of sources (see Chapter 2). It has been well characterized over the years that a number of these individual components are mutagenic, and carcinogenic (Claxton and Woodall, 2007; Claxton et al., 2004). The 2009 PM ISA noted that animal toxicological studies did not focus on specific PM size fractions, but instead emissions from various sources. The 2009 PM ISA concluded that ambient urban PM, emissions from wood smoke and coal combustion, and gasoline exhaust and DE are mutagenic, while PAHs are genotoxic. This conclusion is consistent with previous studies that demonstrated ambient PM and PM from specific combustion sources are mutagenic and genotoxic (U.S. EPA, 2009). Recent studies examined specific $PM_{2.5}$ components and in some cases related those components to specific sources to evaluate whether individual $PM_{2.5}$ components or sources are more closely related to lung cancer mortality and incidence, as well as DNA methylation, than $PM_{2.5}$ mass.

Thurston et al. (2013) in the National Particle Component and Toxicity (NPACT) study, which focused on the ACS-CPS II cohort, examined associations with individual $PM_{2.5}$ components and lung cancer mortality, and only observed evidence of positive associations with Se, a coal combustion tracer, and S. The authors used factor analysis and absolute principal component analysis (APCA) to identify source-related groupings and source categories, respectively. The results of the factor and source-apportionment analyses, which found positive associations with a Coal Combustion source, are consistent with the single-pollutant $PM_{2.5}$ component analyses. Thurston et al. (2013) did not observe evidence of clear associations with lung cancer mortality for any of the other source categories or tracer elements. (quantitative results not presented). The ESCAPE study also examined associations between long-term exposure to $PM_{2.5}$ components and lung cancer mortality. Raaschou-Nielsen et al. (2016) examined associations with eight $PM_{2.5}$ components (Cu, Fe, K, Ni, S, Si, V, and Zn) estimated using LUR methods. Positive associations were observed with all $PM_{2.5}$ components (with the exception of V), albeit with wide confidence intervals, with HR ranging from 1.02 to 1.34 for an IQR increase in $PM_{2.5}$ component concentrations.

Instead of focusing on traditional $PM_{2.5}$ components, Weichenthal et al. (2016) in the CanCHEC cohort examined the association between $PM_{2.5}$ oxidative burden (the product of mass concentration and oxidative potential) and lung cancer mortality. Regional time-weighted $PM_{2.5}$ (2012–2013) average oxidative potential was assessed according to the ability of filter extracts to deplete glutathione and ascorbate in synthetic respiratory tract lining fluid (percent depletion/μg). As detailed previously, there was a positive association with $PM_{2.5}$ mass that was found to be stronger in terms of magnitude and precision when using the glutathione-related $PM_{2.5}$ oxidative burden exposure metric (HR per IQR change in $PM_{2.5}$ and glutathione-related oxidative potential = 1.12 [95% CI: 1.05, 1.19]). There was no

association with ascorbate-related $PM_{2.5}$ oxidative burden (HR per IQR change in $PM_{2.5}$ and ascorbate-related oxidative potential = 0.97 [95% CI: 0.93, 1.01]).

In addition to studies that examined associations between $PM_{2.5}$ components and lung cancer mortality and incidence, a few studies examined whether specific $PM_{2.5}$ components are more strongly related to DNA methylation. Madrigano et al. (2011) within the Normative Aging Study discussed previously, also examined associations between individual $PM_{2.5}$ components and DNA methylation. In addition to $PM_{2.5}$ mass, the authors also observed associations for a reduction in methylation when examining BC and SO_4, particularly in LINE-1, but 95% confidence intervals were large. Additional studies conducted within the Beijing Truck Driver Air Pollution Study cohort detailed previously, also examined the influence of individual $PM_{2.5}$ components on DNA methylation. Hou et al. (2014) examined whether specific $PM_{2.5}$ components (i.e., Al, Ca, Fe, K, S, Si, Ti, and Zn) altered methylation of the same tandem repeats examined in Guo et al. (2014). The authors observed when examining associations for 10% increase in each component that there was evidence of an increase in SATα methylation for S in office workers and in NBL2 methylation for Si and Ca in truck drivers. However, Hou et al. (2014) did not examine components that comprised a larger percentage of $PM_{2.5}$ mass. For example, both Si and Ca represented less than 2 and 1% of the total $PM_{2.5}$ mass exposure for truck drivers and office workers, respectively. The authors reported no evidence of associations with other elemental components (Al, K, Ti, Fe, and Zn) or a difference in the methylation of the tandem repeat D4Z4. Sanchez-Guerra et al. (2015) also examined the Beijing Truck Driver Air Pollution Study cohort, but as detailed above focused on methylation of both 5mC and 5hmC. The authors did not report any evidence of an increase in 5hmC for the components examined in Hou et al. (2014) as well as BC.

Overall, the studies that examined associations between long-term exposure to $PM_{2.5}$ components and sources and lung cancer mortality are consistent with previous evaluations that have indicated that components and sources related to combustion activities are mutagenic and genotoxic and provide biological plausibility for PM-related lung cancer incidence and mortality (U.S. EPA, 2009). Additionally, initial evidence indicates that $PM_{2.5}$ oxidative potential may be an important metric to consider in the future. The limited number of studies that examined associations between exposure to $PM_{2.5}$ components and DNA methylation as well as the limited number of components examined, did not provide consistent evidence that any one component altered DNA methylation.

10.2.7 Summary and Causality Determination

It has been well characterized in toxicological studies that ambient air has mutagenic properties (Claxton et al., 2004) and that extracts of PM from ambient air have carcinogenic properties (Claxton and Woodall, 2007). However, at the completion of the 2009 PM ISA, little information was available from studies employing specific PM size fractions, such as $PM_{2.5}$, or inhalation exposure. The evidence indicating that PM was both a mutagen and carcinogen was supported by epidemiologic evidence of

primarily positive associations in studies of lung cancer mortality, with limited evidence for lung cancer incidence and other cancers. Since the 2009 PM ISA, a larger number of cohort studies using both traditional and more refined exposure assignment approaches provide evidence that primarily consists of positive associations between $PM_{2.5}$ exposure and both lung cancer mortality and lung cancer incidence, which is supported by subset analyses focusing on never smokers. In addition, $PM_{2.5}$ exhibits several key characteristics of carcinogens (Smith et al., 2016), as shown in toxicological studies demonstrating genotoxic effects, oxidative stress, electrophilicity, and epigenetic alterations, with supportive evidence provided by epidemiologic studies. Furthermore, $PM_{2.5}$ has been shown to act as a tumor promoter in a rodent model of urethane-initiated carcinogenesis. This biological plausibility, in combination with the epidemiologic evidence for $PM_{2.5}$ and lung cancer mortality and incidence, contributes to the conclusion of a likely to be causal relationship between long-term $PM_{2.5}$ exposure and cancer. This section describes the evaluation of evidence for cancer, with respect to the causality determination for long-term exposure to $PM_{2.5}$ using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015). The key evidence, as it relates to the causal framework, is summarized in Table 6-34.

Table 10-8 Summary of evidence for a likely to be causal relationship between long-term $PM_{2.5}$ exposure and cancer.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Consistent epidemiologic evidence from multiple, high quality studies at relevant $PM_{2.5}$ concentrations	Increases in lung cancer mortality and incidence in cohort studies conducted in the U.S., Canada, Europe, and Asia. Supported by subset analyses reporting positive associations in never smokers.	Section 10.2.5.1.1 Figure 10-3	Annual: U.S. and Canada: 6.3–23.6 Europe: 6.6–31.0 Asia: 33.7 Table 10-4
Limited epidemiologic evidence from copollutant models for an independent $PM_{2.5}$ association	Potential copollutant confounding for lung cancer mortality and incidence examined in a few studies with initial evidence that associations remained robust in models with O_3, with more limited information for other gaseous pollutants and particle size fractions.	Section 10.2.5.1.3	—
Epidemiologic evidence supports a linear, no-threshold concentration-response (C-R) relationship	Recent multicity studies conducted in the U.S., Canada, and Europe provide evidence of a linear, no-threshold C-R relationship for annual $PM_{2.5}$ concentrations observed within the U.S., but extensive systematic evaluations of alternatives to linearity have not been conducted.	Section 10.2.5.1.4	—

Table 10 8 (Continued): Summary of evidence for a likely to be causal relationship between long term $PM_{2.5}$ exposure and cancer.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Extensive evidence for biological plausibility	Experimental studies provide evidence for oxidative stress in human subjects while in vivo inhalation studies in rodents indicate oxidative DNA damage and methylation of a tumor suppressor gene promotor in the lung, upregulation of enzymes involved in biotransformation, and tumor promotion in a model of urethane-induced tumor initiation. Studies conducted in vitro show formation of DNA adducts, DNA damage, formation of micronuclei, oxidative stress, altered methylation of repetitive elements and miRNAs, increased telomerase activity, mutagenicity, and increased metastatic potential. Additionally, there is supporting epidemiologic evidence for micronuclei formation.	Liu et al. (2015) Soberanes et al. (2012) Yoshizaki et al. (2016) Cangerana Pereira et al. (2011) Section 10.2.1 Section 10.2.2 Section 10.2.3 Section 10.2.4 Section 10.2.5	238 µg/m^3 100–120 µg/m^3 594 µg/m^3 17.66 µg/m^3
Coherence of cancer-related effects across disciplines	Epidemiologic evidence that is coherent with experimental evidence for DNA adduct formation, DNA damage, cytogenetic effects, and altered DNA methylation	Li et al. (2014); Rossner et al. (2013b) Chu et al. (2015) Rossner et al. (2011) O'Callaghan-Gordo et al. (2015) Section 10.2.3	115.4 12.0–78.9 68.4–146.6 26.1–28.4 14.4

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

Experimental and epidemiologic studies provide evidence indicating the potential role of $PM_{2.5}$ exposure in genotoxicity through an examination of cancer-related biomarkers, such as mutagenicity, DNA damage, and cytogenetic endpoints. Decades of research has laid a foundation supporting the mutagenic potential of PM. It has been clearly demonstrated in the Ames *Salmonella*/mammalian-microsome mutagenicity assay that PM contains mutagenic agents (Section 10.2.2.1). Although mutagenicity does not necessarily equate to carcinogenicity, the ability of PM to elicit mutations provides support for observations of an association with lung cancer mortality and incidence in epidemiologic studies. Both in vitro and in vivo toxicological studies indicate the potential for $PM_{2.5}$ exposure to result in DNA damage (Section 10.2.2.2), which is supported by limited evidence from epidemiologic panel studies (Chu et al., 2015) and findings of oxidative stress in a controlled human exposure study (Liu et al., 2015). When examining cytogenetic effects, a limited number of epidemiologic

and toxicological studies provides coherence for micronuclei formation and chromosomal abnormalities (Section 10.2.2.3). Additionally, there was limited evidence for differential expression of genes that may be relevant to cancer pathogenesis. Across scientific disciplines, a broad array of biomarkers of genotoxicity were examined, which complicates the assessment of whether there was evidence for coherence of effects, but overall these studies provide some evidence of a relationship between $PM_{2.5}$ exposure and genotoxicity. Similarly, experimental and epidemiologic studies that examined epigenetic effects indicate changes in methylation, both hyper- and hypomethylation, globally as well as in some specific genomic sites, providing some support for $PM_{2.5}$ exposure contributing to genomic instability (Section 10.2.3). Toxicological evidence that the promoter region of a tumor suppressor gene, p16, was methylated in lung tissue as a result of inhalation exposure to $PM_{2.5}$ is consistent with one of the hallmarks of cancer (Hanahan and Weinberg, 2000); (Hanahan and Weinberg, 2011), i.e., the evading of growth suppressors (Section 10.2.3.1).

The experimental and epidemiologic evidence for genotoxicity and mutagenicity, as well as epigenetic effects, provides biological plausibility for a relationship between exposure to $PM_{2.5}$ and cancer development. In addition, $PM_{2.5}$ exposure enhanced tumor formation in an animal model of urethane-induced tumor initiation (Cangerana Pereira et al., 2011). This study supports a role for $PM_{2.5}$ exposure in tumor promotion, which is a measure of carcinogenic potential. Further substantiating the link between $PM_{2.5}$ exposure and cancer development are epidemiologic studies demonstrating primarily consistent positive associations between long-term $PM_{2.5}$ exposure and lung cancer mortality and incidence across studies using different exposure assignment methods (Section 10.2.5.1). The evidence of $PM_{2.5}$-related lung cancer mortality and incidence is further supported by a number of studies that examined associations by smoking status and reported generally positive associations in never smokers. Across studies, potential confounding by smoking status and exposure to SHS was adequately controlled through either direct measures of smoking status or by using proxy measures to adjust for smoking. Of those studies that did not report evidence of a positive association, only Lipsett et al. (2011) in the CTS cohort examined associations by smoking status for lung cancer mortality and also reported evidence of a positive, albeit imprecise, association in never smokers. A number of the studies focusing on lung cancer incidence examined associations by histological subtype, which allows for an assessment of adenocarcinoma, the only lung cancer subtype found in nonsmokers. Across studies that examined histological subtypes, there was some evidence of positive associations with adenocarcinomas, but associations were imprecise (i.e., wide confidence intervals) and often also observed for other subtypes.

A limited number of recent lung cancer mortality and incidence studies conducted analyses to assess potential copollutant confounding and reported that $PM_{2.5}$ associations were relatively unchanged in models with O_3. However, there was a more limited assessment of potential copollutant confounding by other gaseous pollutants and particle size fractions (Section 10.2.5.1.3). Recent assessments of the C-R relationship between long-term $PM_{2.5}$ exposure and lung cancer mortality and incidence provide evidence of a linear, no-threshold relationship, specifically at concentrations representative of the lowest cut-point examined in studies, 9–11.8 $\mu g/m^3$, and where analyses of the C-R curve depict a widening of confidence

intervals, ≈6 μg/m^3. However, in assessing the C-R relationship, epidemiologic studies have not conducted empirical evaluations of potential alternatives to linearity (Section 10.2.5.1.4).

In addition to lung cancer mortality and incidence, a number of recent studies examined cancers of other sites including breast cancer, brain cancer, liver cancer, and leukemia. Across the studies, the evidence does not clearly depict an association with other types of cancers (Section 10.2.5.2). However, emerging evidence examining cancer survival in people diagnosed with various stages of different types of cancers including respiratory cancer, lung cancer, breast cancer, and liver cancer indicate that long-term $PM_{2.5}$ exposure may contribute to reduced cancer survival, particularly in individuals with less advanced cancer diagnoses (Section 10.2.5.3).

Collectively, experimental and epidemiologic studies provide evidence for a relationship between $PM_{2.5}$ exposure and genotoxicity, epigenetic effects, and carcinogenic potential. Uncertainties exist due to the lack of consistency in specific cancer-related biomarkers associated with $PM_{2.5}$ exposure across both experimental and epidemiologic studies, however $PM_{2.5}$ exhibits several characteristics of carcinogens. This provides biological plausibility for $PM_{2.5}$ exposure contributing to cancer development. **Overall, the combination of this evidence is sufficient to conclude that a causal relationship is likely to exist between long-term $PM_{2.5}$ exposure and cancer**.

10.3 $PM_{10-2.5}$ Exposure and Cancer

The 2009 PM ISA concluded that the overall body of evidence was "inadequate to assess the relationship between long-term $PM_{10-2.5}$ exposures and cancer" (U.S. EPA, 2009).[77] This conclusion was based on the lack of epidemiologic studies that examined $PM_{10-2.5}$ exposure and cancer in both the 2004 PM AQCD and the 2009 PM ISA.

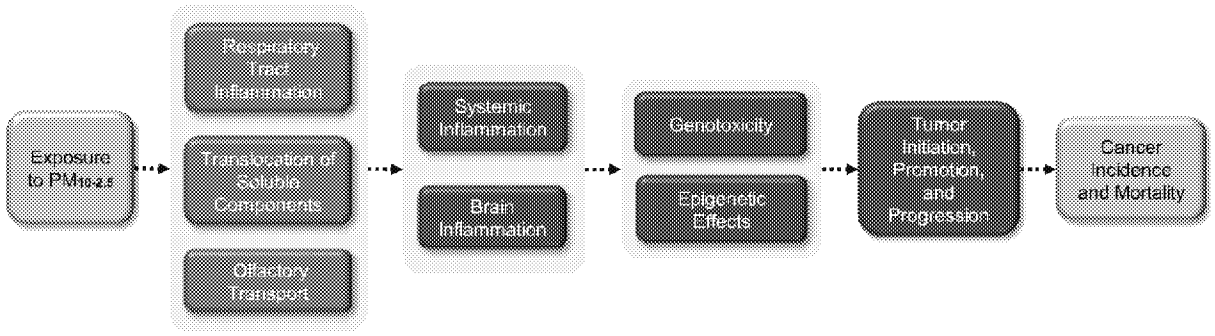
Consistent with the 2009 PM ISA, there remains a limited number of both experimental and epidemiologic studies that examined $PM_{10-2.5}$ exposure and whether it can lead to mutagenicity, genotoxicity, and carcinogenicity, as well as to cancer mortality. Although there is some evidence that $PM_{10-2.5}$ exposure can lead to changes in cancer-related biomarkers, there is a lack of epidemiologic evidence to support the continuum of effects to cancer incidence and mortality. The following sections evaluate studies published since completion of the 2009 PM ISA that focus on the mutagenicity, genotoxicity, and capability of long-term exposures to $PM_{10-2.5}$ to induce epigenetic changes all of which may contribute to cancer incidence and mortality.

[77] As detailed in the Preface, risk estimates are for a 5 μg/m^3 increase in annual $PM_{10-2.5}$ concentrations unless otherwise noted.

10.3.1 Biological Plausibility

This section describes biological pathways that potentially underlie the development of cancer resulting from exposure to $PM_{10-2.5}$. Figure 10-8 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" exposure to $PM_{10-2.5}$ may lead to the development of cancer contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 10.3.

Once $PM_{10-2.5}$ deposits in the respiratory tract, it may be retained, cleared, or solubilized (see Chapter 4). $PM_{10-2.5}$ and its soluble components may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate ROS and this capacity is termed "oxidative potential". Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see Chapter 4). Immune system responses due to the presence of particles in the interstitial space may contribute to chronic health effects. Inflammatory mediators may diffuse from the respiratory tract into the systemic circulation and lead to inflammation in extrapulmonary compartments (see Chapter 6). Although $PM_{10-2.5}$ is mostly insoluble, it may contain some soluble components such as endotoxin and metals. Soluble components of $PM_{10-2.5}$ may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments. A fraction of $PM_{10-2.5}$ may deposit on the olfactory epithelium. Soluble components of $PM_{10-2.5}$ may be transported via the olfactory nerve to the olfactory bulb of the brain. The extent to which translocation into the systemic circulation or transport to the olfactory bulb occurs is currently uncertain. For further discussion of translocation and olfactory transport, see Chapter 4. The potential contribution of olfactory transport to brain inflammation or to upregulation of gene expression in the brain is discussed in Chapter 8.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 10-8 Potential biological pathways for the development of cancer following exposure to $PM_{10-2.5}$.

Evidence is accumulating that exposure to $PM_{10-2.5}$ may lead to carcinogenesis by a genotoxic pathway that may result in mutational events or chromosomal alterations. Carcinogenesis due to dysregulated growth may follow. Compared with $PM_{2.5}$, there is less evidence that $PM_{10-2.5}$ exhibits characteristics of carcinogens (Smith et al., 2016). However, exposure to $PM_{10-2.5}$ has been shown to result in genotoxic effects and to induce oxidative stress. Currently, epidemiologic evidence is limited to studies linking $PM_{10-2.5}$ exposure to lung cancer incidence. Evidence for these pathways and cancer-related biomarkers is described below.

Genotoxicity

Genotoxicity may occur as a result of DNA damage and subsequent introduction of mutations into the genome, and as a result of cytogenetic effects at the level of the chromosome. $PM_{10-2.5}$ exposure is associated with mutagenicity, DNA damage, and cytogenetic effects. Oxidative stress is one mechanisms involved in genotoxicity resulting from $PM_{2.5}$ exposure.

Mutations are considered biomarkers of early biological effect (Demetriou et al., 2012). Indirect evidence is provided by the Ames *Salmonella*/mammalian-microsome mutagenicity assay in one study. It can identify the presence of species that can result in mutations as the result of direct interactions with DNA as well as those that require metabolic activation to elicit genotoxicity. As the most widely accepted theory of cancer etiology is the accumulation of mutations in critical genes, the presence of mutagens within PM provides biological plausibility for observations made in epidemiological studies. While this assay has several technical limitations and is criticized due to its use of bacteria as a model species, four

decades of published results from this assay have clearly demonstrated the presence of mutagenic agents in PM collected from ambient air (U.S. EPA, 2009). A new study published since the 2009 PM ISA provides evidence to support mutagenicity resulting from $PM_{10-2.5}$ exposure (Kawanaka et al., 2008).

DNA damage is a biomarker of genotoxicity (Demarini, 2013). Evidence of DNA damage following $PM_{10-2.5}$ exposure was found using the comet assay in in vitro toxicological studies (Jalava et al., 2015; Wessels et al., 2010). The identification of oxidized DNA bases suggests a role for oxidative stress in the DNA lesions. These oxidized DNA nucleobases are considered a biomarker of exposure (Demetriou et al., 2012). Exposure to PM can result in oxidative stress either through the direct generation of ROS, or indirectly, through the induction of inflammation. Other in vitro studies demonstrated an increase in ROS production as a result of exposure to $PM_{10-2.5}$ (Section 10.3.2). A study in human subjects also found increased oxidized DNA bases in urine in association with $PM_{10-2.5}$ exposure (Liu et al., 2015). The presence of oxidative stress-mediated DNA lesions and adducts can lead to the introduction of fixed mutations into the genome after incorrect repair of the damaged base or replication past the base by low fidelity DNA polymerases. The potential for oxidative stress to result in mutagenesis is underscored by the DNA repair mechanisms that have evolved to protect the genome from mutagenesis caused by these lesions.

Cytogenetic effects, such as micronuclei formation and chromosomal aberrations, are biomarkers of genotoxicity (Demarini, 2013). Micronuclei are nuclei formed as a result of chromosomal damage, while chromosomal aberrations are modifications of the normal chromosome complement (Demetriou et al., 2012). Epidemiologic studies provide supportive evidence of micronuclei formation in association with $PM_{10-2.5}$ exposure (O'Callaghan-Gordo et al., 2015).

Summary of Biological Plausibility

As described here, there is one proposed pathway by which exposure to $PM_{10-2.5}$ may lead to the development of cancer. It involves genotoxicity, including DNA damage that may result in mutational events and cytogenetic effects that may result in effects at the level of the chromosome. While experimental studies in animals and humans contribute most of the evidence of upstream events, epidemiologic studies found associations between exposure to $PM_{10-2.5}$ and micronuclei formation. This proposed pathway provides biological plausibility for epidemiologic results of cancer incidence and mortality and will be used to inform a causality determination, which is discussed later in the chapter (Section 10.3.4).

10.3.2 Genotoxicity

In the 2009 PM ISA, there were a limited number of epidemiologic studies that examined molecular and cellular markers often associated with cancer, which includes both DNA damage and

cytogenetic effects. No studies specifically examined the effects of exposure to $PM_{10-2.5}$. Recent experimental and epidemiologic studies provide a limited body of evidence for genotoxicity due to $PM_{10-2.5}$ exposure.

10.3.2.1 Toxicological Evidence

Very few studies evaluating the genotoxicity and carcinogenicity of $PM_{10-2.5}$ have been published since the 2009 PM ISA. More common are reports detailing the effects in response to PM_{10}. However, as given the scope of the current ISA, only studies detailing the effects of $PM_{10-2.5}$ exposure are summarized here. While the Ames *Salmonella*/mammalian-microsome mutagenicity test was the most common method for analysis of genotoxicity in response to $PM_{2.5}$, the use of human cell culture and other in vitro assays were the primary method for the study of $PM_{10-2.5}$. No new studies published since the 2009 PM ISA that evaluated endpoints related to epigenetic changes in response to ambient air $PM_{10-2.5}$ exposure were identified.

Kawanaka et al. (2008) investigated the mutagenicity of roadside PM organic extracts from Saitama City, Japan. Using a cascade impactor, 12 fractions of varying aerodynamic diameters were collected including $PM_{10-2.5}$ (<0.12, 0.12−0.20, 0.20−0.30, 0.30−0.50, 0.70−1.2, 1.2−2.1, 2.1−3.5, 3.5−5.2, 5.2−7.8, 7.8−11, >11 μm). The authors used the *Salmonella* assay to determine the mutagenic activity of each fraction as well as GC/NCI/MS/MS and known quantities of select nitroaromatic compounds to determine the mass contribution of those compounds to the total PM collected and to estimate the contribution of each species to the total mutagenicity, respectively. Using this approach, it was reported that quantity of nitro-PAHs per unit mass in the ultrafine fraction was greater than that of $PM_{2.5}$ or $PM_{10-2.5}$. In addition, the authors determined that mutagenicity per unit mass of $PM_{10-2.5}$ was less than that of UFP (both TA98 and YG1024 S. Typhimurium strains) and that, of the six nitroaromatic compounds evaluated, the contribution to mutagenic activity calculated was greatest for 1,8-dinitropyrene in all three fractions of PM extracts evaluated. As a result of the variability of the *Salmonella* assay as well as incomplete details regarding the statistical analysis of the data collected, it is difficult to calculate definitive values for these contributions.

Jalava et al. (2015) used the alkaline comet assay to measure DNA damage after exposure to PM suspensions in mouse macrophages (RAW 264.7). They evaluated four size fractions including $PM_{10-2.5}$ collected at Nanjing University in China. The authors observed an increase in damage compared with controls ($p \leq 0.05$), however, the increase was observed only following exposure to the PM suspension of greatest concentration.

Wessels et al. (2010) also characterized the effect of exposure to $PM_{10-2.5}$ in cultured human cells. To represent and compare diverse PM mixture profiles, the authors collected PM from four locations including a rural location and three urban locations that varied in the extent to which vehicle traffic would contribute to the PM mixture sampled. Five size fractions were collected and that with the largest

particles comprised PM with aerodynamic diameters in the range of 3−7 μm. To evaluate the genotoxicity of aqueous PM suspensions, human lung carcinoma epithelial cells (A549) were cultured and used in the formamido-pyrimidine-glycosylase (fpg)-modified comet assay. No differences were observed in the amount of DNA damage induced after exposure to $PM_{10-2.5}$ collected from any of the urban locations compared to that of equal mass collected from the rural location. This is in contrast to the smaller diameter fractions collected for which more DNA damage was observed for several of the urban roadside PM suspension exposures compared to PM collected from the rural site. In addition, the authors determined that, after adjusting for sampling site, the amount of DNA damage measured in response to exposure to different particle size fractions was similar.

Mirowsky et al. (2015), investigated the effects of exposure to aqueous suspensions of both soluble and insoluble material from $PM_{10-2.5}$ as well as $PM_{2.5}$ collected at two rural and three urban sites in California. Using cultured human pulmonary microvasculature endothelial cells (HPMEC-ST11.6R), they measured ROS with 2′,7′-dichlorofluorescein diacetate (DCFH-DA). DCFH-DA, after removal of the acetate groups by cellular esterases, can be oxidized to highly fluorescent DCF that can then be used to quantify the amount of intracellular ROS. The results identified two variables. That is, both the size fraction and location at which the PM was collected can affect the amount of intracellular ROS generated after exposure to aqueous PM suspension. Suspensions from $PM_{10-2.5}$ collected at urban sites were characterized by greater ROS activity than those from $PM_{2.5}$ collected at the same sites ($p < 0.001$). The same disparity was not observed, however, between the $PM_{10-2.5}$ and $PM_{2.5}$ suspensions from the rural sites as the ROS activity generated by both was similar. When comparing the same size fractions between urban and rural sites, greater ROS activity was observed in experiments with $PM_{10-2.5}$ from the urban sites than $PM_{10-2.5}$ collected at the rural sites, while there was not any difference reported between sites for the $PM_{2.5}$ suspensions (p-value not provided).

In the same study, Mirowsky et al. (2015) also used oropharyngeal aspiration to assess the response to aqueous PM suspension exposure in mice (FVB/N). As inflammation and ROS generated by infiltrating polymorphonuclear cells (PMNs) has also been proposed as a pathway that may result in genotoxicity, the authors compared the effect of exposure on the percent of PMNs in lavage fluid for the various sampling locations and PM size fractions. With the exception of one rural location, the increase in percentage of PMNs engendered by exposure to $PM_{10-2.5}$ suspensions was greater than that after exposure to $PM_{2.5}$ ($p < 0.001$).

Gordon et al. (2013) also used the DCFA-FA assay to assess intracellular ROS after exposure to PM. The authors exposed BEAS-2B and HBEpC cells to suspensions of size-fractionated PM from ambient air collected from five diverse sampling locations across the U.S. The PM size fractions collected were described as $PM_{2.5-0.2}$, $PM_{10-2.5}$, and $PM_{0.2}$. Similar to several other findings already highlighted, the authors reported variation in ROS production as a result of sampling site, season, and particle size and noted that exposure to $PM_{10-2.5}$ resulted in ROS production that was less than that of the ultrafine fraction, but greater than that of $PM_{2.5}$ on an equal mass exposure when sampling locations were combined.

10.3.2.2 Evidence from Controlled Human Exposure Studies

A controlled human exposure study by Liu et al. (2015) measured MDA in blood and urine and 8-oxo-dG in urine. The former is a lipid peroxidation product capable of reacting with DNA bases, while the latter is excreted after oxidized dGTP molecules in cellular dNTP pools used for nuclear and mitochondrial DNA replication throughout the cell are acted upon by MTH1 followed by 8-oxo-dGMPase in the process of dNTP pool sanitization. In this single-blind randomized crossover study, nonsmoking adults were exposed for 130 minutes to $PM_{10-2.5}$, $PM_{2.5}$, and UFP CAPs drawn from a downtown street in Toronto, Canada. Participant blood and urine were collected before exposure and after exposure at two-time points (1 hour, 21 hour). A positive association was observed between urinary 8-oxo-dG concentration and concentration of $PM_{10-2.5}$ ($p < 0.1$) at 1-hour post-exposure. Urinary creatinine was used to normalize biomarker concentrations. No association was observed between blood MDA concentration and $PM_{10-2.5}$ concentration.

10.3.2.3 Epidemiologic Evidence

In the Rhea cohort previously detailed in Section 10.2.2, the frequency of micronuclei was examined in 136 mother-child pairs in Crete, Greece (O'Callaghan-Gordo et al., 2015). Within the study, $PM_{10-2.5}$ concentrations (median = 22.5 μg/m^3) were estimated by taking the difference between PM_{10} and $PM_{2.5}$ from monitors at the same location. The pattern of associations observed for exposure to $PM_{10-2.5}$ and micronuclei frequency was similar to that for $PM_{2.5}$, but the magnitude of the association was smaller for $PM_{10-2.5}$. Overall, there was some evidence of a higher micronuclei frequency in maternal blood for an exposure over the entire pregnancy (RR = 1.14 [95% CI 0.94−1.38]), but no evidence of an association for cord blood (RR = 0.96 [95% CI 0.79−1.17]) (O'Callaghan-Gordo et al., 2015). Similar to $PM_{2.5}$, when stratifying by smoking status, an association larger in magnitude was observed in smoking mothers (RR = 1.4 [95% CI: 0.94, 2.1]) compared to nonsmokers (RR = 1.1 [95% CI: 0.86, 1.3]), but 95% confidence intervals crossed the null for both. Additionally, there was evidence that the association between $PM_{10-2.5}$ and micronuclei frequency was increased among women with a lower intake of vitamin C during pregnancy (i.e., <85 ng/day).

10.3.2.4 Summary of Genotoxicity

Evidence that $PM_{10-2.5}$ exposure induces mutagenicity, DNA damage, oxidative DNA damage, and oxidative stress is provided by a limited number of in vitro animal toxicological studies and a single controlled human exposure study. Liu et al. (2015) found oxidative DNA damage following an approximately 2-hour exposure of human subjects to $PM_{10-2.5}$, with rapid but transient increase in a urine biomarker. The tissue source of this marker cannot be discerned so it is unclear where in the body the

DNA damage occurred. Additionally, an epidemiologic study reported evidence of increased micronuclei formation in relation to $PM_{10-2.5}$ exposure (O'Callaghan-Gordo et al., 2015).

10.3.3 Cancer Incidence and Mortality

10.3.3.1 Lung Cancer

At the completion of the 2009 PM ISA, no epidemiologic studies had been conducted that examined the association between long-term $PM_{10-2.5}$ exposure and cancer. Since then, a few studies have examined cancer, but overall the body of evidence is small. As detailed previously, additional studies have examined the overall relationship between long-term exposure to PM and lung cancer by focusing on PM_{10}. However, these PM_{10} studies are not the focus of this evaluation due to their inability to attribute any cancer effects to a specific PM size fraction, such as $PM_{10-2.5}$. A full list of PM_{10} and lung cancer mortality and incidence studies are available at: https://hero.epa.gov/hero/particulate-matter.

10.3.3.1.1 Lung Cancer Incidence

Recent studies that examined the association between long-term $PM_{10-2.5}$ exposure and lung cancer are limited to studies of lung cancer incidence. There were no epidemiologic studies that examined exposures to $PM_{10-2.5}$ and lung cancer mortality. In addition to examining $PM_{10-2.5}$, the studies by Raaschou-Nielsen et al. (2013) in the ESCAPE study and Puett et al. (2014) in the NHS cohort also examined associations with $PM_{2.5}$ as detailed in Section 10.2.2. Study specific details including $PM_{10-2.5}$ concentrations, study population, and exposure assignment approach are presented in Table 10-9.

Table 10-9 Study specific details and $PM_{10-2.5}$ concentrations from recent studies that examined lung cancer incidence.

Study Years	Cohort Location	Years Air Quality/Follow-up	Events/Population	Mean Concentration µg/m³	Exposure Assessment
Lung cancer incidence					
North America					
†Puett et al. (2014)	NHS (U.S.)	$PM_{10-2.5}$: 1988–2007 Follow-up: 1994–2010	Cases: 2,155 Pop: 103,650	8.5[a]	GIS-based spatiotemporal model to each residential address as detailed in Yanosky et al. (2008); $PM_{10-2.5}$ calculated by subtracting monthly PM_{10} and $PM_{2.5}$ estimates
Europe					
†Raaschou-Nielsen et al. (2013)	ESCAPE (Europe)	$PM_{10-2.5}$: 2008–2011 Follow-up: 1990s[b]	Cases: 2,095 Pop: 312,944	Across sites: 4.0–20.8	LUR at geocoded addresses as detailed in Eeftens et al. (2012a); $PM_{10-2.5}$ calculated as the difference between PM_{10} and $PM_{2.5}$ estimates

ESCAPE = European Study of Cohorts for Air Pollution Effects; GIS = Geographic Information System; LUR = Land-Use Regression; NHS = Nurses' Health Study.

[a]Overall 72-mo cumulative average $PM_{10-2.5}$ concentration.

[b]Only 14 or the 17 cohorts were examined for lung cancer, of the cohorts examined initial recruitment started generally in the 1990s with an average follow-up time of 12.8 years.

†Studies published since the 2009 PM ISA.

Both Raaschou-Nielsen et al. (2013) and Puett et al. (2014) estimated $PM_{10-2.5}$ concentrations by subtracting the difference between LUR estimates of PM_{10} and $PM_{2.5}$. As detailed in Section 3.3.2.3, estimating $PM_{10-2.5}$ concentrations by subtracting modeled PM_{10} and $PM_{2.5}$ estimates do not result in the same issues that could occur when subtracting PM_{10} and $PM_{2.5}$ concentrations from collocated monitors. In the ESCAPE study Raaschou-Nielsen et al. (2013) reported an imprecise positive association with $PM_{10-2.5}$ (HR = 1.09 [95% CI 0.88, 1.33]). Puett et al. (2014) in the NHS cohort, which consisted only of women, also reported an imprecise positive association with lung cancer incidence (HR = 1.02 [95% CI: 0.96, 1.10]). Compared to the $PM_{2.5}$ results in both studies, the magnitude of the association was similar for Puett et al. (2014), but for Raaschou-Nielsen et al. (2013) the $PM_{2.5}$ effect was larger in magnitude and more indicative of a relationship with lung cancer incidence.

For Raaschou-Nielsen et al. (2013), unlike the analysis of $PM_{2.5}$ that examined a subset of the cohort that did not change residence during follow-up, a sensitivity analysis was not conducted for $PM_{10-2.5}$ to assess the potential influence of exposure measurement error. Additionally, an analysis by

histological cancer subtype was not conducted for $PM_{10-2.5}$. However, Puett et al. (2014) in the NHS cohort examined associations by smoking status and histological cancer subtype. The authors observed that the association between long-term $PM_{10-2.5}$ exposure and lung cancer incidence was larger in magnitude among never smokers, but 95% confidence intervals were still large (HR = 1.05 [95% CI: 0.86, 1.30]). When focusing specifically on those lung cancer cases defined as adenocarcinoma in the full cohort, the magnitude of the association was larger (HR = 1.11 [95% CI: 0.94, 1.30]) than that observed when focusing on all lung cancer incidence cases.

10.3.3.2 Other Cancers

A few recent studies have examined associations between long-term $PM_{10-2.5}$ exposure and cancer incidence and mortality beyond the respiratory system. This includes individual studies examining breast cancer (Hart et al., 2016) and liver cancer (Pedersen et al., 2017) that reported positive associations, (HR = 1.03 [95% CI: 0.96, 1.10]) and (HR ranging from 1.26−1.86 depending on the ESCAPE cohort), respectively, but with large 95% confidence intervals. Collectively, there are a limited number of studies that examined other cancers and this evidence does not clearly depict an association between long-term $PM_{10-2.5}$ and other cancer sites.

10.3.3.3 Summary

Overall, there is limited evidence of a positive association between long-term $PM_{10-2.5}$ exposure and lung cancer incidence, with no studies examining lung cancer mortality. In both studies that examined lung cancer incidence, $PM_{10-2.5}$ concentrations were estimated by taking the difference between PM_{10} and $PM_{2.5}$ estimates, but these estimates were derived from an LUR model (see Section 3.3.2.3). A few recent studies examined associations with cancers in other sites, but the limited number of studies prevents a full assessment of the relationship between long-term $PM_{10-2.5}$ exposure and cancers in other sites.

10.3.4 Summary and Causality Determination

It has been well characterized in toxicological studies that ambient air has mutagenic properties (Claxton et al., 2004) and that extracts of PM from ambient air have carcinogenic properties (Claxton and Woodall, 2007). However, at the completion of the 2009 PM ISA, little information was available from studies employing specific PM size fractions, such as $PM_{10-2.5}$, or inhalation exposure. Since the 2009 PM ISA, the assessment of long-term $PM_{10-2.5}$ exposure and cancer remains limited with a few recent epidemiologic studies of large and diverse cohorts providing evidence of imprecise positive associations of $PM_{10-2.5}$ with lung cancer incidence. However, uncertainty remains with respect to exposure measurement error due to the methods employed to estimate $PM_{10-2.5}$ concentrations (Section 3.3.2.3),

specifically the use of $PM_{10-2.5}$ predictions that have not been validated by monitored $PM_{10-2.5}$ concentrations. Experimental studies are more limited in number compared with the evaluation of $PM_{2.5}$ and consist of a controlled human exposure study and several in vitro animal toxicological studies demonstrating DNA damage, oxidative stress, and mutagenicity. $PM_{10-2.5}$ exhibits two key characteristics of carcinogens (Smith et al., 2016), as shown in experimental studies demonstrating genotoxic effects and oxidative stress, providing some biological plausibility for epidemiologic findings. The small number of epidemiologic and experimental studies. along with the uncertainty with respect to exposure measurement error, contribute to the determination of the relationship between long-term $PM_{10-2.5}$ exposure and cancer using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015). The key evidence, as it relates to the causal framework, is summarized in Table 10-10. **Overall, the evidence is suggestive of, but not sufficient to infer, a causal relationship between long-term $PM_{10-2.5}$ exposure and cancer**.

Table 10-10 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between long-term $PM_{10-2.5}$ exposure and cancer.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{10-2.5}$ Concentrations Associated with Effects[c]
A limited body of epidemiologic evidence at relevant $PM_{10-2.5}$ concentrations	Positive, but imprecise, increases in lung cancer incidence in a few studies conducted in North America and Europe.	Section 10.3.3.1	U.S.: 8.5 Europe: 4.0–20.8
Uncertainty regarding exposure measurement error	$PM_{10-2.5}$ concentrations estimated by taking the difference between LUR modeled PM_{10} and $PM_{2.5}$ concentrations. Uncertainty remains because $PM_{10-2.5}$ predictions are not validated by monitored $PM_{10-2.5}$ concentrations although PM_{10} and $PM_{2.5}$ LUR model predictions are validated.	Section 3.3.2.3	
Evidence for biological plausibility	Experimental studies provide evidence for oxidative DNA damage in human subjects and DNA damage, oxidative stress, and mutagenicity in vitro. Additional epidemiologic evidence supports micronuclei formation.	Liu et al. (2015) Section 10.3.2.1 O'Callaghan-Gordo et al. (2015)	213 $\mu g/m^3$

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{10-2.5}$ concentrations with which the evidence is substantiated.

10.4 UFP Exposure and Cancer

The 2009 PM ISA concluded that the overall body of evidence was "inadequate to assess the relationship between long-term UFP exposures and cancer." This conclusion was based on the lack of epidemiologic studies that examined UFP exposure and cancer in both the 2004 PM AQCD and the 2009 PM ISA.

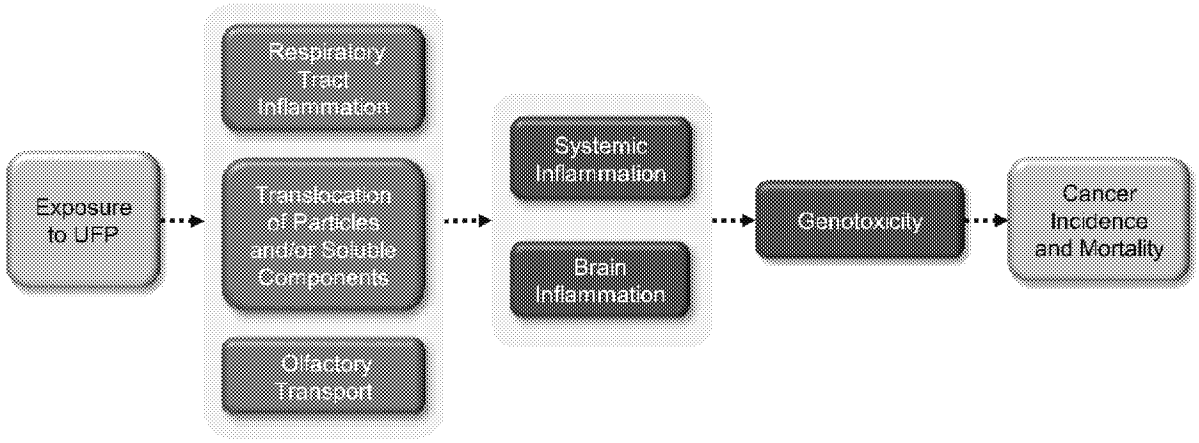
Consistent with the 2009 PM ISA, there remains a limited number of both experimental and epidemiologic studies that examined UFP exposure and whether it can lead to mutagenicity, genotoxicity, and carcinogenicity, as well as to cancer mortality, with no studies of lung cancer incidence or mortality. Although there is some evidence that UFP exposure can lead to changes in cancer-related biomarkers, there is a lack of epidemiologic evidence to support the continuum of effects to cancer incidence and mortality. The following sections evaluate studies published since completion of the 2009 PM ISA that focus on the mutagenicity and, genotoxicity of long-term exposures to UFP, which may contribute to cancer incidence and mortality.

10.4.1 Biological Plausibility

This section describes biological pathways that potentially underlie the development of cancer resulting from exposure to UFP. Figure 10-9 graphically depicts the proposed pathways as a continuum of upstream events, connected by arrows, that may lead to downstream events observed in epidemiologic studies. This discussion of "how" exposure to UFP may lead to the development of cancer contributes to an understanding of the biological plausibility of epidemiologic results evaluated later in Section 0.

Once UFP deposits in the respiratory tract, it may be retained, cleared, or solubilized (see Chapter 4). UFP and its soluble components may interact with cells in the respiratory tract, such as epithelial cells, inflammatory cells, and sensory nerve cells. One way in which this may occur is through reduction-oxidative (redox) reactions. As discussed in Section 2.3.3, PM may generate ROS and this capacity is termed "oxidative potential". Furthermore, cells in the respiratory tract may respond to the presence of PM by generating ROS. Further discussion of these redox reactions, which may contribute to oxidative stress, is found in Section 5.1.1 of the 2009 PM ISA (U.S. EPA, 2009). In addition, poorly soluble particles may translocate to the interstitial space beneath the respiratory epithelium and accumulate in the lymph nodes (see Chapter 4). Immune system responses due to the presence of particles in the interstitial space may contribute to chronic health effects. Inflammatory mediators may diffuse from the respiratory tract into the systemic circulation and lead to inflammation in extrapulmonary compartments (see Chapter 6). UFP and its soluble components may translocate into the systemic circulation and contribute to inflammatory or other processes in extrapulmonary compartments. A fraction of UFP may deposit on the olfactory epithelium. UFP and its soluble components may be transported via the olfactory nerve to the olfactory bulb of the brain. The extent to which translocation

into the systemic circulation or transport to the olfactory bulb occurs is currently uncertain. For further discussion of translocation and olfactory transport, see Chapter 4. The potential contribution of olfactory transport to brain inflammation or to upregulation of gene expression in the brain is discussed in Chapter 8.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below.

Figure 10-9 Potential biological pathways for the development of cancer following exposure to UFP.

Evidence is accumulating that exposure to UFP may lead to carcinogenesis by a genotoxic pathway that may result in mutational events or chromosomal alterations. Carcinogenesis due to dysregulated growth may follow. Compared with $PM_{2.5}$, there is less evidence that UFP exhibits characteristics of carcinogens (Smith et al., 2016). However, exposure to UFP resulted in genotoxic effects and oxidative stress. In addition, exposure to UFP induced genes involved in PAH biotransformation, indicating that UFP contained electrophilic species. Currently there are no epidemiologic studies evaluating the relationship between exposure to UFP and lung cancer, although breast cancer incidence has been studied. Evidence for these pathways and for cancer-related biomarkers is described below.

Genotoxicity

Genotoxicity may occur as a result of DNA damage and subsequent introduction of mutations into the genome, and as a result of cytogenetic effects at the level of the chromosome. UFP exposure is associated with mutagenicity and DNA damage. Mechanisms involved in genotoxicity resulting from UFP exposure include oxidative stress and biotransformation.

Mutations are considered biomarkers of early biological effect (Demetriou et al., 2012). Indirect evidence is provided by the Ames *Salmonella*/mammalian-microsome mutagenicity assay. It can identify the presence of species that can result in mutations as the result of direct interactions with DNA as well as those that require metabolic activation to elicit genotoxicity. As the most widely accepted theory of cancer etiology is the accumulation of mutations in critical genes, the presence of mutagens within PM provides biological plausibility for observations made in epidemiological studies. While this assay has several technical limitations and is criticized due to its use of bacteria as a model species, four decades of published results from this assay have clearly demonstrated the presence of mutagenic agents in PM collected from ambient air (U.S. EPA, 2009). A new study published since the 2009 PM ISA provides evidence to support mutagenicity resulting from UFP exposure (Kawanaka et al., 2008).

DNA damage is a biomarker of genotoxicity (Demarini, 2013). Evidence of DNA damage resulting from exposure to UFP was found using the comet assay which measures single and double DNA strand breaks in vitro (Jalava et al., 2015). The identification of oxidized DNA bases suggests a role for oxidative stress in the DNA lesions. These oxidized DNA nucleobases are considered a biomarker of exposure (Demetriou et al., 2012). Exposure to PM can result in oxidative stress either through the direct generation of reactive oxygen species (ROS), or indirectly, through the induction of inflammation. An in vitro study demonstrated an increase in ROS production as a result of exposure to UFP (Gordon et al., 2013). Studies in human subjects found increased oxidized DNA bases in urine (Liu et al., 2015) and evidence of DNA damage in peripheral blood mononuclear cells (Hemmingsen et al., 2015) in association with UFP exposure. The presence of oxidative stress-mediated DNA lesions and adducts can lead to the introduction of fixed mutations into the genome after incorrect repair of the damaged base or replication past the base by low fidelity DNA polymerases. The potential for oxidative stress to result in mutagenesis is underscored by the DNA repair mechanisms that have evolved to protect the genome from mutagenesis caused by these lesions.

Evidence that genes participating in PAH biotransformation are upregulated as a result of exposure to UFP is provided by an in vitro study (Borgie et al., 2015a). Biotransformation via Cyp1A1 may result in the production of PAH metabolites capable of reacting with DNA to form bulky DNA adducts. As in the case of oxidative stress mediated DNA adducts, when DNA repair of bulky adducts is absent or ineffective, mutational events may occur.

Summary of Biological Plausibility

As described here, there is one proposed pathway by which exposure to UFP may lead to the development of cancer. It involves genotoxicity, including DNA damage that may result in mutational events. Experimental studies in animals and humans contribute all of the evidence of upstream events. This proposed pathway provides biological plausibility for epidemiologic results of cancer incidence and mortality and will be used to inform a causality determination, which is discussed later in the section (Section 10.4.4).

10.4.2 Genotoxicity

10.4.2.1 Toxicological Evidence

Similar to $PM_{10-2.5}$ exposure, very few studies have been published since the 2009 ISA that describe effects relevant to genotoxicity resulting from exposure to UFP.

Kawanaka et al. (2008) investigated the mutagenicity of roadside PM organic extracts from Saitama City, Japan. Using a cascade impactor, 12 fractions of varying aerodynamic diameters were collected including an ultrafine fraction (<0.12). The authors used the *Salmonella* assay to determine the mutagenic activity of each fraction as well as GC/NCI/MS/MS and known quantities of select nitroaromatic compounds to determine the mass contribution of those compounds to the total PM collected and to estimate the contribution of each species to the total mutagenicity, respectively. Using this approach, it was reported that the quantity of nitro-PAHs per unit mass in the ultrafine fraction was greater than that of $PM_{10-2.5}$ or $PM_{2.5}$. In addition, the authors determined that mutagenicity per unit mass of UFP was greater than that of the other two PM size fractions in both TA98 and YG1024 S. Typhimurium strains. Of the six nitroaromatic compounds evaluated, the contribution to mutagenic activity calculated was greatest for 1,8-dinitropyrene in all three fractions of PM extracts evaluated. As a result of the variability of the *Salmonella* assay as well as incomplete details regarding the statistical analysis of the data collected, it is difficult to calculate definitive values for these contributions.

Jalava et al. (2015), as discussed earlier in the $PM_{2.5}$ and $PM_{10-2.5}$ sections, used the alkaline comet assay to measure DNA damage after exposure to PM suspensions in mouse macrophages (RAW 264.7). They evaluated four size fractions including a near ultrafine fraction described as $PM_{0.2}$ collected at Nanjing University in China. Similar to the increase observed after exposure to $PM_{10-2.5}$, the authors observed an increase in damage compared with controls ($p \leq 0.05$), however, the increase was only observed following exposure to the PM suspension of greatest concentration.

Gordon et al. (2013) measured intracellular ROS in BEAS-2B and HBEpC cells using the DCFH-DA assay after exposure to ambient UFP, as well as $PM_{10-2.5}$ and $PM_{2.5}$ size fractions collected

from five diverse sampling locations across the U.S. Similar to several other findings already highlighted, the authors reported variation in ROS production as a result of sampling site, season, and particle size and noted that exposure to the ultrafine fraction resulted in ROS production that was greater than that of both $PM_{10-2.5}$ and $PM_{2.5}$ on an equal mass exposure when sampling locations were combined.

Borgie et al. (2015a) collected ambient PM with aerodynamic diameters near those considered ultrafine (<0.3 μm) from an urban and rural location near Beirut, Lebanon and exposed cultured BEAS-2B cells to extracted organic material from the collected PM as well as intact PM suspension. The authors measured AhR, ARNT, AhRR, CYP1A1, CYP1B1, and NQO1 gene expression. They reported that, generally, an increase in CYP1A1, CYP1B1, and AhRR ($p < 0.05$) mRNA expression was observed compared to controls for both urban and rural sites. These findings are consistent with the results from their study that evaluated $PM_{2.5}$ (Borgie et al., 2015b). In that study, they also observed increases in CYP1A1, CYP1B1, and AhRR gene expression after exposure to $PM_{2.5-0.3}$ suspensions. Notably, while the current study by Borgie et al. (2015a) reported that increases in gene expression were observed for cells exposed to both EOM and aqueous suspensions, the increases in gene expression were generally greater after exposure to EOM compared with PM suspension ($p > 0.05$). This is consistent with the findings noted by Turner et al. (2015).

10.4.2.2 Evidence from Controlled Human Exposure Studies

Controlled human exposure studies have also evaluated various markers relevant to DNA damage. Hemmingsen et al. (2015) identified an association between combined DNA strand breaks and FPG sensitive sites in peripheral blood mononuclear cells and total particle number concentration using a mixed effects analysis ($p = 0.016$). These measures were representative of nonoxidative and oxidative DNA damage, respectively. In contrast, no evidence of oxidative stress or DNA damage was found in relation to $PM_{2.5}$ concentration. As described in Section 10.2.2.2, this controlled, cross-over, repeated measures human exposure study was carried out in central Copenhagen, Denmark in overweight, older adults who were exposed for 5 hours in chambers with and without high efficiency particulate adsorption filters.

A controlled human exposure study by Liu et al. (2015) measured MDA in blood and urine and 8-oxo-dG in urine. The former is a lipid peroxidation product capable of reacting with DNA bases, while the latter is excreted after oxidized dGTP molecules in cellular dNTP pools used for nuclear and mitochondrial DNA replication throughout the cell are acted upon by MTH1 followed by 8-oxo-dGMPase in the process of dNTP pool sanitization. In this single-blind randomized crossover study, nonsmoking adults were exposed for 130 minutes to $PM_{10-2.5}$, $PM_{2.5}$, and UFP CAPs drawn from a downtown street in Toronto, Canada. Participant blood and urine were collected before exposure and after exposure at two time points (1 hour, 21 hour). A positive association was observed between urinary 8-oxo-dG concentration and UFP concentration ($p < 0.05$) at 1-hour post-exposure. Urinary creatinine

was used to normalize biomarker concentrations. No association was observed between blood MDA concentration and concentration of UFP.

10.4.2.3 Summary of Genotoxicity

Evidence that UFP exposure induces mutagenicity, DNA damage, oxidative DNA damage, oxidative stress, and upregulation of enzymes involved in biotransformation is provided by a limited number of in vitro animal toxicological studies and two controlled human exposure study. Hemmingsen et al. (2015) identified an association between DNA damage in peripheral blood mononuclear cells and total particle number concentration. Liu et al. (2015) found oxidative DNA damage following an approximately 2-hour exposure of human subjects to UFP, with rapid but transient increase in a marker in urine. The tissue source of this marker cannot be discerned so it is unclear where in the body the DNA damage occurred. There were no epidemiologic studies that evaluated genotoxicity and carcinogenicity in relation to UFP exposure.

10.4.3 Cancer Incidence and Mortality

At the completion of the 2009 PM ISA, there were no studies that examined the association between long-term UFP exposure and lung cancer incidence or mortality or cancers in other sites. The only recent study that has focused on cancer and UFPs is a study conducted by Goldberg et al. (2017) in Montreal, Canada that examined postmenopausal breast cancer incidence. In a population-based, case-control study where UFP exposures from a LUR were assigned at geocoded addresses or centroids of postal codes the authors reported no evidence of an association in a model controlling for all individual-level covariates (OR = 1.02 [95% CI: 0.93, 1.13] for a 3,461.9 cm^{-3} increase in UFPs).

10.4.4 Summary and Causality Determination

It has been well characterized in toxicological studies that ambient air has mutagenic properties (Claxton et al., 2004) and that extracts of PM from ambient air have carcinogenic properties (Claxton and Woodall, 2007). However, at the completion of the 2009 PM ISA, little information was available from studies employing specific PM size fractions, such as UFP, or inhalation exposure. Since the 2009 PM ISA, a single epidemiologic study evaluated breast cancer incidence and found no evidence to support this outcome. Furthermore, no epidemiologic studies evaluated lung cancer in association with UFP exposure. Experimental studies are few in number and consist of a few controlled human exposure studies and in vitro animal toxicological studies. UFP exhibits two key characteristics of carcinogens (Smith et al., 2016) by demonstrating genotoxic effects and oxidative stress in experimental studies. While there is some biological plausibility for exposure to UFP and cancer, there is a lack of epidemiologic evidence of

cancer incidence or mortality. Additionally, there is uncertainty in the spatial variability of long-term UFP exposures, which is compounded by the relatively sparse UFP monitoring data in the U.S. This section describes the evaluation of evidence for cancer, with respect to the causality determination for long-term exposures to UFP using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015). The key evidence, as it relates to the causal framework, is summarized in Table 10-11. **Overall, the evidence is inadequate to infer the presence or absence of a causal relationship between long-term UFP exposure and cancer**.

Table 10-11 Summary of evidence that is inadequate to infer the presence or absence of a causal relationship between long-term UFP exposure and cancer.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	UFP Concentrations Associated with Effects[c]
Lack of epidemiologic evidence at relevant UFP concentrations	Assessment of cancer limited to a study of breast cancer that reported no evidence of an association	Section 10.4.3	—
Uncertainty regarding exposure measurement error	Limited data on UFP concentrations over time and the spatial variability of UFP concentrations across urban areas	Section 2.5.1.1.5 Section 2.5.1.2.4 Section 2.5.2.2.3 Section 3.4.5	
Limited evidence for biological plausibility	Experimental studies provide evidence for oxidative DNA damage in human subjects while in vitro studies indicate DNA damage, oxidative stress, upregulation of enzymes involved in biotransformation, and mutagenicity	Hemmingsen et al. (2015) Liu et al. (2015) Kawanaka et al. (2008) Section 10.4.2	23,000/cm^2 136 µg/m^3

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the UFP concentrations with which the evidence is substantiated.

10.5 References

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CHAPTER 11 MORTALITY

Summary of Causality Determinations for Short- and Long-Term PM Exposure and Total (Nonaccidental) Mortality

This chapter characterizes the scientific evidence that supports causality determinations for short- and long-term PM exposure and total mortality. The types of studies evaluated within this chapter are consistent with the overall scope of the ISA as detailed in the Preface (see Section P 3.1). In assessing the overall evidence, strengths and limitations of individual studies were evaluated based on scientific considerations detailed in the Appendix. More details on the causal framework used to reach these conclusions are included in the Preamble to the ISA (U.S. EPA, 2015b).

Size Fraction	Causality Determination
Short-term exposure	
$PM_{2.5}$	Causal
$PM_{10-2.5}$	Suggestive of, but not sufficient to infer
UFP	Inadequate
Long-term exposure	
$PM_{2.5}$	Causal
$PM_{10-2.5}$	Suggestive of, but not sufficient to infer
UFP	Inadequate

11.1 Short-Term $PM_{2.5}$ Exposure and Total Mortality

The 2009 Integrated Science Assessment for Particulate Matter (hereafter 2009 PM ISA) concluded that "a causal relationship exists between short-term exposure to $PM_{2.5}$ and mortality" (U.S. EPA, 2009).[78] This conclusion was based on the evaluation of both multi- and single-city studies that further supported the consistent positive associations between short-term $PM_{2.5}$ exposure and mortality (i.e., total [nonaccidental] mortality) observed in the 2004 PM AQCD, with associations for total (nonaccidental) mortality ranging from 0.29% (Dominici et al., 2007) to 1.2% (Franklin et al., 2007). These associations were strongest, in terms of magnitude and precision, primarily at lags within the range of 0–1 days. Although an examination of the potential confounding effects of gaseous copollutants was

[78] As detailed in the Preface, risk estimates are for a 10 μg/m^3 increase in 24-hour avg $PM_{2.5}$ concentrations, unless otherwise noted.

limited in the studies evaluated in the 2009 PM ISA, evidence from single-city studies evaluated in the 2004 PM AQCD indicated that gaseous copollutants have minimal effect on the $PM_{2.5}$-mortality relationship. The evaluation of cause-specific mortality found that risk estimates were larger in magnitude, but also had larger confidence intervals, for respiratory mortality compared to cardiovascular mortality. Although the largest mortality risk estimates were for respiratory mortality, the interpretation of the results was complicated by the limited coherence from studies of respiratory morbidity. However, the evidence from studies of cardiovascular morbidity provided both coherence and biological plausibility for the relationship between short-term $PM_{2.5}$ exposure and cardiovascular mortality.

The multicity studies evaluated in the 2009 PM ISA provided initial information with respect to seasonal patterns of associations and city-to-city heterogeneity in $PM_{2.5}$-mortality risk estimates along with potential factors that may explain some of this heterogeneity. An evaluation of $PM_{2.5}$-mortality risk estimates by season indicated that associations tend to be largest in magnitude during the spring. Additionally, multicity studies demonstrated a regional pattern in associations with the magnitude being larger in the Eastern U.S., but also indicated that nationally, and even within a region, there are differences among city-specific $PM_{2.5}$-mortality risk estimates. Although not systematically considered across the studies evaluated in the 2009 PM ISA, several studies examined factors that provided some evidence that may explain the heterogeneity in $PM_{2.5}$-mortality risk estimates observed both within and across studies, including exposure factors (e.g., air-conditioning use), demographic differences, and $PM_{2.5}$ composition.

An evaluation of the concentration-response (C-R) relationship and whether a threshold exists was limited to multicity studies of PM_{10}. Collectively, the multicity studies that examined the C-R relationship between short-term PM_{10} exposure and mortality reported evidence of a linear, no-threshold relationship. However, some studies that also examined the C-R relationship for individual cities provided initial evidence indicating potential city-to-city differences in the shape of the C-R curve.

In addition to examining the association between short-term $PM_{2.5}$ exposures and mortality with a focus on PM mass, a few multicity studies examined whether specific $PM_{2.5}$ components modified the $PM_{2.5}$-mortality relationship while other studies focused on examining whether individual $PM_{2.5}$ components or PM sources were more strongly associated with mortality than $PM_{2.5}$ mass. In many cases, the evaluation of $PM_{2.5}$ components was limited due to the rather sparse temporal data coverage as a result of the every 3rd or 6th day sampling schedule of monitors. Collectively, these studies did not provide evidence that any one component or source is more strongly associated with mortality, which is consistent with the larger body of literature that examined the relationship between $PM_{2.5}$ components and sources and other health effects (U.S. EPA, 2009).

As detailed in the Preface , the focus of this section is on the evaluation of recently published studies that directly address policy-relevant issues, i.e., those studies where mean 24-hour average concentrations are less than 20 $\mu g/m^3$ across all cities or where at least half of the cities have mean 24-hour average concentrations less than 20 $\mu g/m^3$. Additionally, consistent with previous ISAs, this

section focuses primarily on multicity studies because they examine the association between short-term $PM_{2.5}$ exposure and a health effect over a large geographic area that consists of diverse atmospheric conditions and population demographics, using a consistent statistical methodology, which avoids the potential publication bias often associated with single-city studies (U.S. EPA, 2008). However, where applicable single-city studies, as well as multicity studies with mean 24-hour average concentrations greater than 20 $\mu g/m^3$, are evaluated when they: encompass a long study-duration; examine whether a specific population or lifestage may be at increased risk of $PM_{2.5}$-related mortality (see Chapter 12); or further characterize the relationship between short-term $PM_{2.5}$ exposure and mortality (e.g., copollutant analyses) not represented in the multicity studies with mean 24-hour average concentrations less than 20 $\mu g/m^3$ (U.S. EPA, 2016, 2015a). Other recent studies that do not fit the criteria mentioned above are not the focus of this section, and are available at: https://hero.epa.gov/hero/particulate-matter.

The following sections provide a brief overview of the consistent, positive associations observed in recent studies of mortality and short-term $PM_{2.5}$ exposures, with the main focus on assessing the degree to which these studies further characterize the relationship between short-term $PM_{2.5}$ exposure and mortality detailed in the 2009 PM ISA (U.S. EPA, 2009). The multicity, as well as single-city studies, discussed throughout this section, along with study-specific details and air quality characteristics are highlighted in**Error! Reference source not found.** Table 11-1 and represent those studies that attempt to further characterize the $PM_{2.5}$-mortality evidence by examining: potential confounding (i.e., copollutants and seasonal/temporal trends); effect modification (e.g., stressors, pollutants, season); geographic heterogeneity in associations; shape of the C-R relationship and related issues (e.g., threshold, lag structure of associations); and the relationship between $PM_{2.5}$ components and sources and mortality.

Table 11-1 Study-specific details and $PM_{2.5}$ concentrations from multicity studies in the 2004 PM Air Quality Criteria Document (AQCD) and 2009 PM ISA, and recent multicity studies.

Study/Location Years	Mortality Outcome(s)	Exposure Assessment	Mean Concentration $\mu g/m^3$	Upper Percentile Concentrations $\mu g/m^3$	Copollutant Examination
North America					
Burnett and Goldberg (2003)[a] Eight Canadian cities (1986–1996)	Total	One monitor in each of six cities and average of two monitors in two cities	13.3	98th: 38.9 99th: 45.4 Max: 86.0	Correlation (*r*): NA Copollutant models with: NA

Table 11-1 (Continued): Study-specific details and $PM_{2.5}$ concentrations from multicity studies in the 2004 PM Air Quality Criteria Document (AQCD) and 2009 PM ISA, and recent multicity studies.

Study/Location Years	Mortality Outcome(s)	Exposure Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
Klemm and Mason (2003)[a] 6 U.S. cities (1979–1988)	Total	One monitor in each city	14.7[b]	75th: 23.0 95th: 43.3	Correlation (*r*): NA Copollutant models with: NA
Burnett et al. (2004) 12 Canadian cities (1981–1999)	Total	Average of multiple monitors in each city	12.8	98th: 38.0 99th: 45.0 Max: 86.0	Correlation (*r*): 0.48 NO_2 Copollutant models with: NO_2
Ostro et al. (2006) 9 CA counties, U.S. (1999–2002)	Total Cardiovascular Respiratory	One monitor or average of multiple monitors in each county	19.9	98th: 38.9 99th: 45.4 Max: 160.0	Correlation (*r*): 0.56 NO_2; 0.60 CO; −0.14 1-h O_3; −0.22 8-h O_3 Copollutant models with: NA
Franklin et al. (2008) 25 U.S. cities (2000–2005)	Total Cardiovascular Respiratory	One monitor or average of multiple monitors in each city using method detailed in Schwartz (2000)	14.8	98th: 43.0 99th: 50.9 Max: 239.2	Correlation (*r*): NA Copollutant models with: NA
Franklin et al. (2007) 27 U.S. cities (1997–2002)	Total Cardiovascular Respiratory	One monitor or average of multiple monitors in each city using method detailed in Schwartz (2000)	15.6	98th: 45.8 99th: 54.7 Max: 239.0	Correlation (*r*): NA Copollutant models with: NA
Dominici et al. (2007) 96 U.S. cities (NMMAPS) (1999–2000)	Total Cardiovascular Respiratory	10% trimmed mean of all monitors in a city	---	---	Correlation (*r*): NA Copollutant models with: NA
Zanobetti and Schwartz (2009) 112 U.S. cities (1999–2005)	Total Cardiovascular Respiratory	One monitor or average of multiple monitors in each city using method detailed in Schwartz (2000)	13.2	98th: 34.3 99th: 38.6 Max: 57.4	Correlation (*r*): NA Copollutant models with: $PM_{10-2.5}$

Table 11-1 (Continued): Study-specific details and $PM_{2.5}$ concentrations from multicity studies in the 2004 PM Air Quality Criteria Document (AQCD) and 2009 PM ISA, and recent multicity studies.

Study/Location Years	Mortality Outcome(s)	Exposure Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
†Di et al. (2017a) U.S. (2000–2012)	All-cause	Daily predictions to 1km x 1 km grid using combination of monitoring data, satellite measurements and other data as detailed in Di et al. (2016) and Di et al. (2017b); R^2 = 0.84	---	---	Correlation (*r*): NA Copollutant models with: O_3
†Lippmann et al. (2013a) 148 U.S. cities (2001–2006)	Total Cardiovascular Respiratory	One monitor or average of multiple monitors in each city using method detailed in Schwartz (2000)	7.9[b]	---	Correlation (*r*): NA Copollutant models with: NA
†Zanobetti et al. (2014b)[d] 121 U.S. cities (1999–2010)	All-cause	One monitor or average of multiple monitors in each city using method detailed in Schwartz (2000)	4.37–17.97c	---	Correlation (*r*): NA Copollutant models with: NA
†Baxter et al. (2017) 77 U.S. Cities (2001–2005)	Total	One monitor or average of multiple monitors in each city, when multiple monitors uncorrelated monitors ($r < 0.8$) excluded	Cluster 1: 13.0 Cluster 2: 13.6 Cluster 3: 12.2 Cluster 4: 14.1 Cluster 5: 13.7	Max: Cluster 1: 19.9 Cluster 2: 16.2 Cluster 3: 22.7 Cluster 4: 16.6 Cluster 5: 14.9	Correlation (*r*): NA Copollutant models with: NA
†Dai et al. (2014) 75 U.S. cities (2000–2006)	Total Cardiovascular MI Stroke Respiratory	One monitor or average of multiple monitors in each city	13.3	---	Correlation (*r*): NA Copollutant models with: NA

Table 11-1 (Continued): Study-specific details and $PM_{2.5}$ concentrations from multicity studies in the 2004 PM Air Quality Criteria Document (AQCD) and 2009 PM ISA, and recent multicity studies.

Study/Location Years	Mortality Outcome(s)	Exposure Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
†Krall et al. (2013) 72 U.S. cities (2000–2005)	Total	One monitor or arithmetic mean of all monitors in each city	13.6	Max: 22.8	Correlation (*r*): NA Copollutant models with: NA
†Kloog et al. (2013) New England, U.S. (2000–2008)	Total	Daily predictions to 10 km × 10 km grid using combination of satellite measurements, monitor data, and LUR detailed in Kloog et al. (2011); R^2 = 0.84 (temporal)	9.8	75th: 11.9	Correlation (*r*): NA Copollutant models with: NA
†Shi et al. (2015)[d] New England, U.S. (2003–2009)	All-cause	Daily predictions to 1 km × 1 km grid using combination of satellite measurements, monitor data, and LUR detailed in Kloog et al. (2014); R^2 = 0.87 (temporal)	8.2	75th: 10.6 Max: 53.9	Correlation (*r*): NA Copollutant models with: NA
†Lee et al. (2015c) Three southeastern states, U.S. (North Carolina, South Carolina, Georgia) (2007–2011)	Total Cardiovascular Stroke CHF MI Respiratory	Daily predictions to 1 km x 1 km grid cell using combination of satellite measurements, monitor data, and LUR detailed in Lee et al. (2015b); R^2 = 0.70–0.81	11.1	Max: 86.2	Correlation (*r*): NA Copollutant models with: NA
†Young et al. (2017) California (2000–2012)[e]	Total	Highest reporting monitor on each day in each air basin	12.5–36.7[f]	NR	Correlation (*r*): NA Copollutant models with: NA

Table 11-1 (Continued): Study-specific details and $PM_{2.5}$ concentrations from multicity studies in the 2004 PM Air Quality Criteria Document (AQCD) and 2009 PM ISA, and recent multicity studies.

Study/Location Years	Mortality Outcome(s)	Exposure Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
Europe					
†Janssen et al. (2013) Netherlands (2008–2009)	Total Cardiovascular Respiratory	Nationwide average of 10 monitors	16.3	75th: 20.9 Max: 106.1	Correlation (*r*): 0.95 PM_{10}; 0.29 $PM_{10-2.5}$ Copollutant models with: $PM_{10-2.5}$
†Pascal et al. (2014) Nine French cities (2001–2006)	Total Cardiovascular Cerebrovascular Respiratory	Average of all monitors in each city	13–18[c]	Max: 68–111	Correlation (*r*): >0.80 (across cities) PM_{10}; <0.40 (across cities) $PM_{10-2.5}$; >0.7 (during summer across cities) O_3 Copollutant models with: O_3, $PM_{10-2.5}$
†Samoli et al. (2013) 10 European Mediterranean cities (MED-PARTICLES) (2001–2010)	Total Cardiovascular Respiratory	Average of all monitors in each city	13.6–27.7[b,c]	75th: 18.8–48.0	Correlation (*r*): 0.2–0.7 $PM_{10-2.5}$; 0.3–0.8 NO_2; <0.6 SO_2; <0.6 O_3 Copollutant models with: SO_2, NO_2, O_3, $PM_{10-2.5}$
†Lanzinger et al. (2016) Five Central European cities (UFIREG) (2011–2014)	Total Cardiovascular Respiratory	Average of all monitors in each city	14.9–20.7[f]	Max: 78.8–114.8	Correlation (*r*): 0.55–0.73 NO_2; 0.93–0.97 PM_{10}; 0.40–0.61 $PM_{10-2.5}$; 0.25–0.37 UFP; 0.49–0.50 PNC Copollutant models with: NA
†Stafoggia et al. (2017)[g] Eight European cities (1999–2013)	Total Cardiovascular Respiratory	Average of all monitors in each city	8.0–23.0	NA	Correlation (*r*): 0.09–0.56 UFP Copollutant models with: NA

Table 11-1 (Continued): Study-specific details and $PM_{2.5}$ concentrations from multicity studies in the 2004 PM Air Quality Criteria Document (AQCD) and 2009 PM ISA, and recent multicity studies.

Study/Location Years	Mortality Outcome(s)	Exposure Assessment	Mean Concentration µg/m³	Upper Percentile Concentrations µg/m³	Copollutant Examination
Asia					
†Lee et al. (2015a) 11 East Asian cities (2001–2009)	Total Cardiovascular Respiratory	Average of all monitors in each city	17.7–69.9[c]	75th: 24.1–106.8	Correlation (*r*): NA Copollutant models with: SO_2, NO_2, O_3, $PM_{10-2.5}$
†Ueda et al. (2009) 20 Japanese areas (2002–2004)	Total	1 monitor in each area	11.8–22.8[c]	90th: 21.5–38.2	Correlation (*r*): 0.55 NO_2; 0.10 O_x Copollutant models with: NA

ACE = acute coronary events; CAPES = China Air Pollution and Health Effects Study; CHF = congestive heart failure; MI = myocardial infarction; NMMAPS = National Morbidity, Mortality, and Air Pollution Study; O_x = photochemical oxidants; UFIREG = Ultrafine Particles—an evidence based contribution to the development of regional and European environmental and health policy.

[a]Multicity studies included in the 2004 PM AQCD.

[b]Median concentrations.

[c]Range of mean concentrations across all cities.

[d]Only had data for all-cause mortality including accidental mortalities, focused analyses on total (nonaccidental) mortality.

[e]Due to the sparsity of data for year 2000, it was excluded from the main analysis.

[f]Young et al. (2017) only reported average $PM_{2.5}$ concentrations for each year and not an average across all years; therefore this range represents the minimum and maximum concentration reported in any year across all air basins.

[g]Only 4 of the 5 cities had $PM_{2.5}$ data.

[h]Stafoggia et al. (2017) did not report quantitative estimates for cardiovascular and respiratory mortality.

†Studies published since the 2009 PM ISA.

11.1.1 Biological Plausibility for Short-Term $PM_{2.5}$ Exposure and Total (Nonaccidental) Mortality

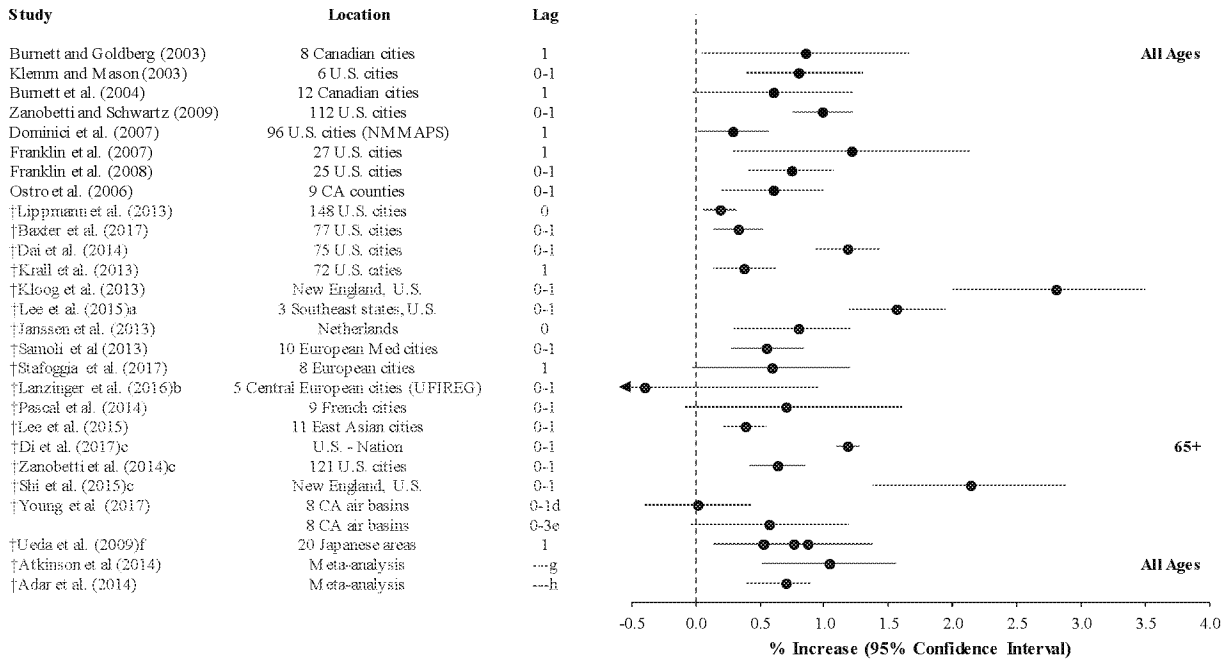
The preceding chapters characterized evidence related to evaluating the biological plausibility by which short-term $PM_{2.5}$ exposure may lead to the morbidity effects that are the largest contributors to total (nonaccidental) mortality, specifically cardiovascular and respiratory morbidity (Section 6.1.1 and Section 5.1.1, respectively). This evidence is derived from animal toxicological, controlled human exposure, and epidemiologic studies. Section 6.1.1 outlines the available evidence for plausible mechanisms by which inhalation exposure to $PM_{2.5}$ could progress from initial events to endpoints relevant to the cardiovascular system and to population outcomes such as emergency department (ED) visits and hospital admissions due to cardiovascular disease, particularly ischemic heart disease and congestive heart failure. Similarly, Section 5.1.1 characterizes the available evidence by which inhalation exposure to $PM_{2.5}$ could progress from initial events to endpoints relevant to the respiratory system.

However, the evidence for how the initial events and subsequent endpoints could lead to the observed increases in respiratory ED visits and hospital admissions, for particularly chronic obstructive pulmonary disease (COPD) and asthma, is limited. Collectively, the progression demonstrated in the available evidence for cardiovascular morbidity (and to a lesser extent, respiratory morbidity) supports potential biological pathways by which short-term $PM_{2.5}$ exposures could result in mortality.

11.1.2 Associations between Short-Term $PM_{2.5}$ Exposure and Total (Nonaccidental) Mortality in All-Year Analyses

In previous PM reviews, specifically the 2004 PM AQCD (U.S. EPA, 2004) and the 2009 PM ISA (U.S. EPA, 2009), the number of multicity studies that examined the association between short-term $PM_{2.5}$ exposure and total (nonaccidental) mortality was rather limited with the largest body of evidence encompassing single-city studies. The single-city studies evaluated in previous reviews were conducted in diverse geographic locations and reported primarily consistent positive associations between $PM_{2.5}$ exposure and daily mortality. The limited number of large multicity studies included in those reviews could be attributed to the rather small sample of ambient $PM_{2.5}$ monitoring data available at that time with the majority of monitoring being initiated in the years 1999 and 2000. Recent multicity studies encompass a larger number of years and sometimes include daily $PM_{2.5}$ concentrations, whereas previous studies were often limited to a shorter time series and $PM_{2.5}$ data that was only collected every 3rd or 6th day.

Recent multicity studies conducted across the U.S., Canada, Europe, and Asia, as well as meta-analyses (Adar et al., 2014; Atkinson et al., 2014) that examined a larger number of studies of short-term $PM_{2.5}$ exposures and mortality, primarily report consistent positive associations within the range of risk estimates reported in the 2009 PM ISA (i.e., 0.19% (Lippmann et al., 2013a) to 2.80% (Kloog et al., 2013)) (Figure 11-1). An exception to this trend across multicity studies is Lanzinger et al. (2016), which as part of the "ultrafine particles—an evidence based contribution to the development of regional and European environmental and health policy" or UFIREG study observed no evidence of an association between short-term $PM_{2.5}$ exposure and total (nonaccidental) mortality. The results of the UFIREG study may be a reflection of the short time series for each city included in the study (i.e., approximately 2 years), compared to the other multicity studies that consisted of longer study durations as summarized in Table 11-1. Additionally, in contrast to Ostro et al. (2006), a recent study by Young et al. (2017) did not provide any evidence of an association between short-term $PM_{2.5}$ exposure and mortality when examining eight air basins in California. The difference in results between these two studies could be attributed to: (1) the larger spatial domain over which exposure was assigned in Young et al. (2017), i.e., an air basin (encompassing multiple counties), compared to Ostro et al. (2006), i.e., a single county; (2) the use of only the highest monitor on each day to assign exposure Young et al. (2017) versus the averaging of all monitors over the spatial domain examined Ostro et al. (2006); and (3) the statistical models used in both studies.



NMMAPS = National Morbidity, Mortality, and Air Pollution Study; UFIREG = Ultrafine Particles—an evidence based contribution to the development of regional and European environmental and health policy.

[a]Results are from modeled $PM_{2.5}$ analysis, analysis focusing on measured $PM_{2.5}$ reported 1.21% (95% CI: 0.94, 1.47).

[b]Only four of the five cities measured $PM_{2.5}$.

[c]Shi et al. (2015) and Zanobetti et al. (2014b) only had data for all-cause mortality including accidental mortalities.

[d]Main model used in Young et al. (2017) included current and average of 3 previous days daily maximum temperature, daily minimum temperature, and maximum daily relative humidity.

[e]Sensitivity analysis in Young et al. (2017) focusing on only the San Fransisco Bay air basin, dropping out the maximum daily relative humidity term, where the shortest duration of lag days examined was 0−3 days.

[f]Ueda et al. (2009) presented results for three different modeling approaches, which are presented here: GAM, GLM, and case-crossover.

[g]Atkinson et al. (2014) primarily focused on single-day lag results.

[h]Adar et al. (2014) focused on single-day lag results, specifically lag 0, 1, or 2.

Note: †Studies published since the 2009 PM ISA. Black circles = U.S. and Canadian multicity studies evaluated in the 2004 PM AQCD and 2009 PM ISA. Red circles = Multicity studies and meta-analyses published since the completion of the 2009 PM ISA. Corresponding quantitative results are reported in the Supplemental Material for this chapter, see (U.S. EPA, 2018a).

Figure 11-1 Summary of associations between short-term $PM_{2.5}$ exposure and total (nonaccidental) mortality in multicity studies for a 10 μg/m^3 increase in 24-hour average concentrations.

11.1.2.1 Examination of $PM_{2.5}$-Mortality Relationship through Causal Modeling Statistical Approaches

In addition to traditional epidemiologic study designs (e.g., time-series, case-crossover), there has been a growing interest in applying causal modeling statistical approaches to examine the $PM_{2.5}$-mortality relationship. Within the studies that examined short-term $PM_{2.5}$ exposure and mortality, two types of

causal modeling approaches have been employed: (1) causal inference (Schwartz et al., 2017; Schwartz et al., 2015) and (2) quasi-experimental (Yorifuji et al., 2016) (Table 11-2).

Table 11-2 Methods and results from epidemiologic studies that applied causal inference statistical approaches.

Study	Method	Results
Causal inference		
†Schwartz et al. (2015) Boston, MA (2004–2009)	Instrumental variable: used back trajectories of $PM_{2.5}$ along with variables for wind speed and sea level pressure in a 2-stage approach to develop temperature independent predictions of daily $PM_{2.5}$ concentrations (the instrument). Analyses used 2-day mean instrument concentrations.	0.53% (95% CI: 0.09, 0.97) for a 1 μg/m^3 increase in the instrument for $PM_{2.5}$
	Propensity score: modeled $PM_{2.5}$ in a linear regression with variables for time, temperature, day of week, and copollutants (O_3, NO_2, SO_2, and CO). The predicted $PM_{2.5}$ concentrations from the model represent the propensity score. After trimming days with highest and lowest 5% propensity scores, divided the scores into deciles. Analyses used 2-day mean predicted $PM_{2.5}$ concentrations.	0.50% (95% CI: 0.2, 0.8) for a 1 μg/m^3 increase in $PM_{2.5}$
	Sensitivity analysis: using an approach similar to Granger causality, the instrumental variable was used to examine the association between the instrument 2 days after the day of death on today's value of daily deaths.	Failed to reject null hypothesis, (P = 0.93; 95% CI: −0.43, 0.47)
†Schwartz et al. (2017) Boston, MA (2000–2009)	Instrumental variable: planetary boundary layer (PBL) and wind speed at lag 0 and lag 1 were regressed on $PM_{2.5}$, BC or NO_2 concentrations to generate a single instrumental variable for each pollutant representative of local pollution, taking into consideration variation within month-by-year strata and within deciles of temperature. Analyses used 2-day mean instrument concentrations.	0.90% (95% CI: 0.25, 1.56) for an IQR increase in the instrument for local $PM_{2.5}$
	Sensitivity analysis: using an approach similar to Granger causality, the instrumental variable was used to examine the association between the instrument 2 and 3 days after the day of death on today's value of daily deaths.	0.18% (95% CI: −0.45, 0.81) for an IQR increase in the instrument for local $PM_{2.5}$

Table 11-2 (Continued): Methods and results from epidemiologic studies that applied causal inference statistical approaches.

Study	Method	Results
Quasi-experimental		
†Yorifuji et al. (2016) Tokyo, Japan (2000–2012)	Compared mortality rates in Tokyo, Japan, which had a strict diesel emissions control ordinance in place and Osaka, Japan, which did not. Interrupted time-series analysis used to regress log of age-standardized mortality rates in Tokyo, weighted by daily trends in Osaka, on the $PM_{2.5}$ concentrations and estimated rate ratios across 3-year intervals using the three years prior to the ordinance as a reference period.	Difference in mortality between 2000–2003 and 2009–2012: Total: −6.0% Cardiovascular: −11.0% IHD: −10.0% Cerebrovascular: −6.2% Pulmonary: −22.0%

BC = black carbon, IHD = ischemic heart disease.

†Studies published since the 2009 PM ISA.

Through causal inference statistical approaches, the goal is to "estimate the difference (or ratio) in the expected value of [an] outcome in the population under the exposure they received versus what it would have been had they received an alternative exposure" (Schwartz et al., 2015). Schwartz et al. (2015) and Schwartz et al. (2017) examined instrumental variable and propensity score approaches using data from Boston, MA. Through the instrumental variable approach, a variable is constructed that is only related to the outcome through the exposure of interest, while the propensity score approach represents the conditional probability of exposure assignment given a vector of observed covariates (Schwartz et al., 2015).

Schwartz et al. (2015) and Schwartz et al. (2017) took different approaches to constructing instrumental variables, and both reported evidence of an association between the $PM_{2.5}$ instrument and mortality (Table 11-2). In Schwartz et al. (2017) this association was found to persist when limiting the analysis to days with 24-hour average $PM_{2.5}$ concentrations <30 $\mu g/m^3$ (0.84% [95% CI: 0.19, 1.50]). Schwartz et al. (2015) and Schwartz et al. (2017) also conducted Granger-like causality tests to examine whether there was evidence of an association between mortality and $PM_{2.5}$ concentrations after the day of death, which would support the possibility that unmeasured confounders were not accounted for in the statistical model. Both Schwartz et al. (2015) and Schwartz et al. (2017) reported no evidence of an association with $PM_{2.5}$ concentrations measured after death.

While Schwartz et al. (2015) and Schwartz et al. (2017) focused on causal inference approaches that result in the development of alternative exposure variables, Yorifuji et al. (2016) conducted a quasi-experimental study that examined whether a specific regulatory action in Tokyo, Japan (i.e., a diesel emission control ordinance) resulted in a subsequent reduction in daily mortality (Table 11-2). The quasi-experimental design relies on some intervention that is meant to reduce ambient air pollution

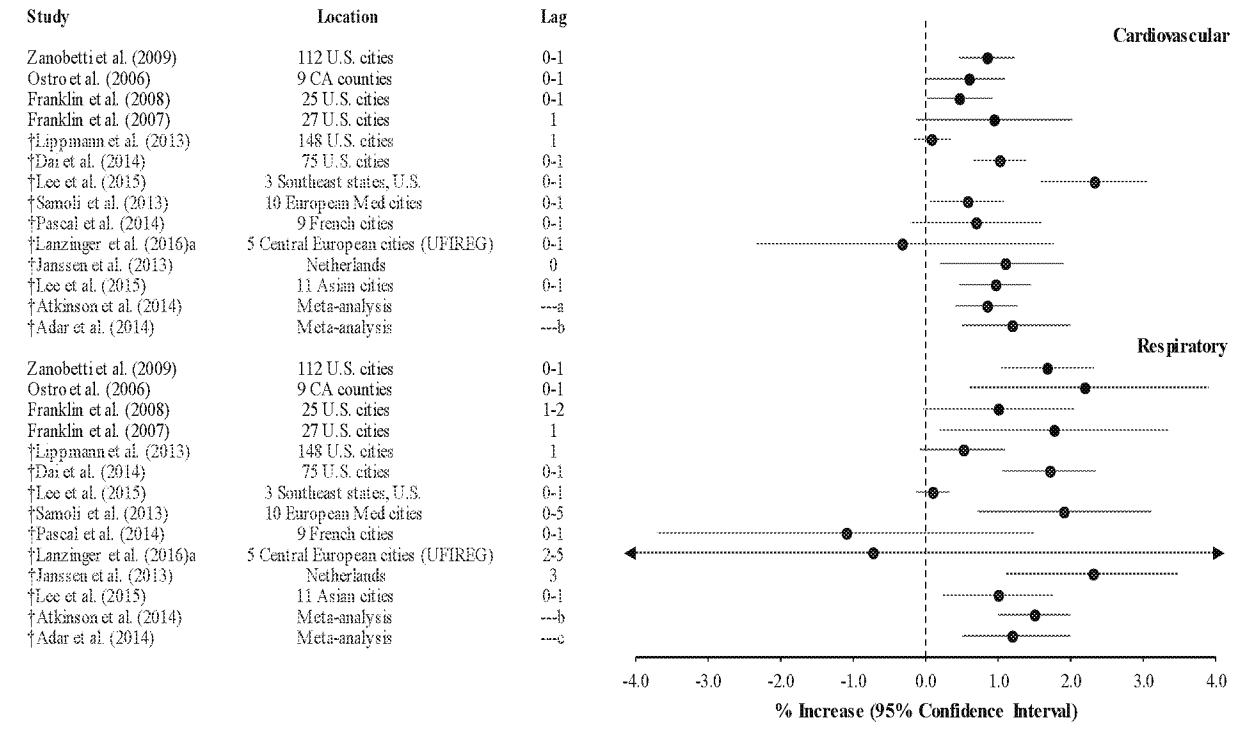
concentrations. Yorifuji et al. (2016) reported evidence of a reduction in mortality in Tokyo due to the ordinance, in comparison to Osaka, Japan, which did not have a similar diesel emission control ordinance in place.

Although the studies to date that have used causal modeling statistical approaches are limited to two locations, overall the studies provide additional support for the relationship between short-term $PM_{2.5}$ exposure and mortality described in previous and recent studies, including those highlighted in Figure 11-1. Additionally, the study by Yorifuji et al. (2016) demonstrates that improvements in air quality, including reductions in $PM_{2.5}$ concentrations, contribute to public health benefits such as reductions in daily mortality.

11.1.3 Associations between Short-Term $PM_{2.5}$ and Cause-Specific Mortality in All-Year Analyses

Single and multicity studies evaluated in the 2009 PM ISA that examined cause-specific mortality reported consistent positive associations with both cardiovascular and respiratory mortality. The magnitude of the association was larger for respiratory mortality, but also had greater confidence intervals due to the smaller number of respiratory-related deaths compared to cardiovascular-related deaths.

Recent multicity studies have further examined the relationship between short-term $PM_{2.5}$ exposure and cause-specific mortality, with some studies conducting additional examinations of specific cardiovascular or respiratory deaths (e.g., stroke, COPD as mentioned in Section 5.1.9 and Section 6.1.9). These studies generally report positive associations, which is consistent with the studies evaluated in the 2009 PM ISA. Overall, these studies report larger risk estimates for respiratory mortality, but many of the confidence intervals are larger than those for cardiovascular mortality due to cardiovascular mortality representing a greater percentage of total mortality (~35%) compared to respiratory mortality (<10%) (American Heart Association, 2011) (Figure 11-2). A more thorough discussion of cardiovascular- and respiratory-related mortality can be found in the respective cardiovascular and respiratory effects sections (Section 5.1.9 and Section 6.1.9).



UFIREG = Ultrafine Particles—an evidence-based contribution to the development of regional and European environmental and health policy.

[a]Only four of the five cities measured $PM_{2.5}$.

[b]Atkinson et al. (2014) primarily focused on single-day lag results.

[c]Adar et al. (2014) focused on single-day lag results, specifically lag 0, 1, or 2.

Note: †Studies published since the 2009 PM ISA. Studies organized by lag structure, therefore, cardiovascular and respiratory mortality results are not in the same order. Black circles = U.S. and Canadian multicity studies evaluated in the 2004 PM AQCD and 2009 PM ISA. Red circles = Multicity studies and meta-analyses published since the completion of the 2009 PM ISA.

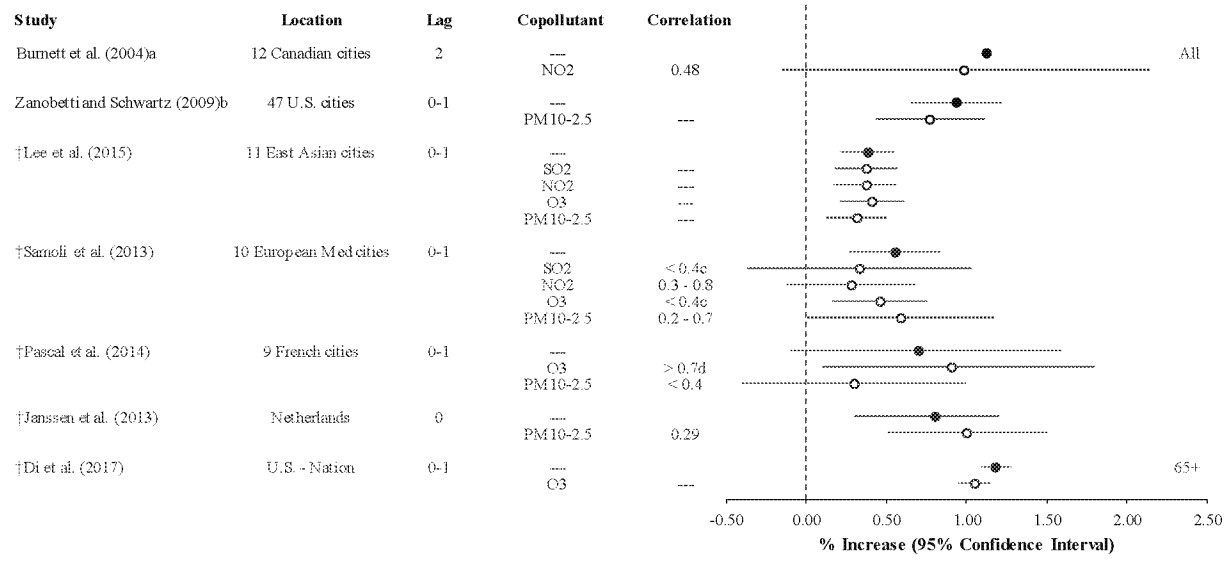
Corresponding quantitative results are reported in the Supplemental Material for this chapter, see (U.S. EPA, 2018a).

Figure 11-2 Summary of associations between short-term $PM_{2.5}$ exposure and cardiovascular and respiratory mortality in multicity studies for a 10 µg/m^3 increase in 24-hour average concentrations.

11.1.4 Potential Copollutant Confounding of the $PM_{2.5}$-Mortality Relationship

Analyses of potential copollutant confounding of the $PM_{2.5}$-mortality relationship in the 2009 PM ISA indicated that associations remain robust, and relatively unchanged in copollutant models. These conclusions were based primarily on a multicity study conducted in Canada (Burnett et al., 2004) along with single-city studies reviewed in the 2004 PM AQCD (U.S. EPA, 2004), and supporting evidence from studies that examined the PM_{10}-mortality relationship. Recent multicity studies that assess the potential for copollutant confounding of the $PM_{2.5}$-mortality relationship are limited to Europe and Asia. However, similar to the 2004 PM AQCD and 2009 PM ISA, analyses of potential confounding by gaseous pollutants (i.e., SO_2, NO_2, and O_3) were limited in number, with additional analyses focusing on copollutant models with $PM_{10-2.5}$. Overall, studies that examined potential copollutant confounding reported that $PM_{2.5}$-mortality risk estimates remained positive and relatively unchanged in models with both gaseous pollutants and $PM_{10-2.5}$, although confidence intervals increased in some cases. Across studies that examined potential confounding by gaseous copollutants (Di et al., 2017a; Lee et al., 2015a; Pascal et al., 2014; Samoli et al., 2013), the $PM_{2.5}$-mortality relationship was relatively unchanged (Figure 11-3). Those studies that present correlation coefficients provide additional information to support the results from the copollutant analyses due to the low ($r < 0.4$) to moderate correlations ($r = 0.4 < 0.7$) observed.

When assessing the evidence across the studies that examined potential copollutant confounding by $PM_{10-2.5}$, the approaches used to estimate $PM_{10-2.5}$ varied across studies, which could contribute to exposure measurement error and complicate the overall interpretation of results (Section 3.3.1.1). However, regardless of the method used to estimate $PM_{10-2.5}$ concentrations, in copollutant models the $PM_{2.5}$-mortality association was relatively unchanged, but in some cases confidence intervals were larger compared to the single pollutant models (Figure 11-3). The results from multicity studies that examined potential confounding of the $PM_{2.5}$-mortality relationship by $PM_{10-2.5}$ are further supported by a meta-analysis conducted by Adar et al. (2014). The authors focused almost exclusively on the $PM_{10-2.5}$-mortality relationship, but also examined $PM_{2.5}$. In copollutant analyses the authors observed that $PM_{2.5}$-mortality associations were relatively unchanged when including $PM_{10-2.5}$ in the model (quantitative results not presented).



[a]Data from 1998–2000 when PM measured by TEOM. Standard error for the single-pollutant $PM_{2.5}$ result was not reported in the study so only the central estimate is included.

[b]Analysis focused on 112 U.S. cities, but $PM_{10-2.5}$ only measured in 47 U.S. cities.

Note: †Studies published since the 2009 PM ISA. Closed circles = single-pollutant results. Open circles = copollutant results. Corresponding quantitative results are reported in the Supplemental Material for this chapter. See (U.S. EPA, 2018a).

Figure 11-3 Summary of association between short-term $PM_{2.5}$ exposure and total (nonaccidental) mortality for a 10 μg/m^3 increase in 24-hour average concentrations in single- and copollutant models from previous and recent multicity studies.

11.1.5 Other Potential Confounders of the $PM_{2.5}$-Mortality Relationship

11.1.5.1 Long-Term Temporal Trends and Weather

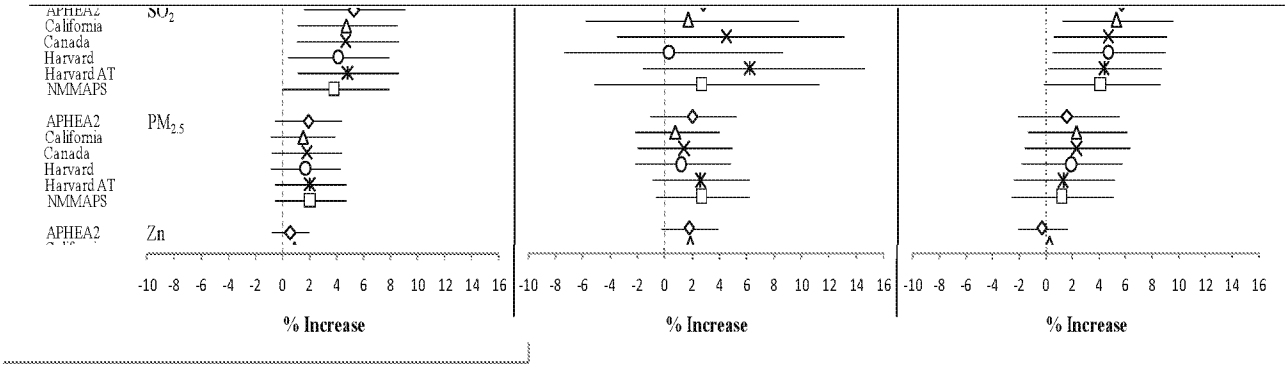
In the 2009 PM ISA, studies that examined the influence of alternative model specification, in terms of controlling for temporal trends or the confounding effects of weather were limited to studies of PM_{10}. Of these studies Welty and Zeger (2005) conducted the most systematic evaluation and found that PM_{10}-mortality risk estimates remained robust across various combinations of degrees of freedom (df) to control for temporal trends and weather covariates. At the completion of the 2009 PM ISA, there were not studies of short-term $PM_{2.5}$ exposure and mortality that conducted similar analyses to address whether the results observed in PM_{10} studies were consistent for $PM_{2.5}$. Recent multicity, as well as a few single-city, studies specifically examined the influence of model specification on the $PM_{2.5}$-mortality association

while others conducted sensitivity analyses to examine whether the primary statistical model was appropriate.

Ueda et al. (2009) in a study of 20 Japanese cities and Sacks et al. (2012) in a study in Philadelphia, PA conducted systematic evaluations of alternative models to adjust for long-term temporal trends and weather covariates. Ueda et al. (2009) examined a generalized additive model (GAM), generalized linear model (GLM), and logistic regression through a case-crossover analysis to examine the relationship between short-term air pollution exposure, including $PM_{2.5}$, and mortality. Across models, the $PM_{2.5}$-mortality association remained relatively unchanged after increasing the df employed (i.e., 3 or 6) to control for the potential nonlinear relationship between ambient temperature and mortality. These results are consistent with Lee et al. (2015c) in a study of three southeastern U.S. states where the $PM_{2.5}$-mortality association remained robust when increasing the df for the temperature covariate from 2 to 4.

In Ueda et al. (2009), the largest influence on the $PM_{2.5}$-mortality association was observed for the GLM when changing the approach to adjust for seasonality from using an indicator variable of every 2 months to the more traditional approach of using a natural spline. The results using the natural spline in the GLM (0.43% [95% CI: 0.00, 0.86]; lag 1) were more consistent with those observed in the GAM (0.53% [95% CI: 0.13, 0.94]; lag 1) where penalized splines were used to adjust for seasonality. It is worth noting that overall the results of the comparisons conducted by Ueda et al. (2009) are consistent with previous analyses that have shown that the GLM, GAM, and case-crossover approach all result in relatively consistent results (Schwartz et al., 2003).

Sacks et al. (2012) took a different approach than Ueda et al. (2009) by examining the influence of model specification using the models employed in recent multicity studies conducted by Burnett and Goldberg (2003), Zanobetti and Schwartz (2009), Zanobetti and Schwartz (2008), Ostro et al. (2008), Samoli et al. (2005), and Dominici et al. (2005) within the context of a similar data set. These models differed by the approach used to control for long-term temporal trends (i.e., number of df per year) and the potential confounding effects of weather (i.e., the weather covariate included in the model, and the accompanying lag and/or df for the covariate). Focusing on daily cardiovascular mortality and daily air pollution concentrations, including $PM_{2.5}$, the authors observed in all-year analyses that results for $PM_{2.5}$ were relatively similar across models with the percent increase in cardiovascular mortality ranging from 1.5–2.0% (Figure 11-4). In seasonal analyses there was more variability in the magnitude of the association across models (i.e., cold Season: 1.2–2.3%; warm Season: 0.8–2.7%), but the direction of the association remained consistent.



Note: APHEA2 = Samoli et al. (2005); California = Ostro et al. (2008); Canada = Burnett and Goldberg (2003); Harvard = Zanobetti and Schwartz (2009); Harvard AT = Zanobetti and Schwartz (2008); and NMMAPS = Dominici et al. (2005).
Source: Permission pending, Sacks et al. (2012).

Figure 11-4 Percent increase in cardiovascular mortality for a 10 μg/m^3 increase in 24-hour average $PM_{2.5}$ concentrations at lag 0–1 in Philadelphia, PA (May 1992–September 1995) across statistical models used in multicity studies.

Whereas Ueda et al. (2009) and Sacks et al. (2012) conducted systematic evaluations on the influence of model specification on the $PM_{2.5}$-mortality relationship, other studies conducted more targeted analyses. Lee et al. (2015a) and Samoli et al. (2013) in 11 East Asian cities and 10 European Mediterranean cities, respectively, both examined the influence of various approaches to control for long-term temporal trends on the $PM_{2.5}$-mortality relationship. In sensitivity analyses where the df employed per year ranged from 6 to 12, Lee et al. (2015a) did not observe any evidence that $PM_{2.5}$-mortality risk estimates changed as the df increased. Samoli et al. (2013) examined alternative approaches to control for long-term temporal trends through either setting the df a priori, using absolute sum of the residuals of the partial autocorrelation function (PACF) or a case-crossover design in the context of a Poisson model with a three-way interaction. Across each approach, the authors observed that the magnitude of the association was smallest when specifying the df per year to use a priori, but a positive association persisted across all approaches ranging from 0.55 to 0.97%.

In the Denver Aerosol Sources and Health (DASH) study, Kim et al. (2015) further confirmed the results from previous studies that examined alternative specifications to account for long-term temporal trends and the confounding effects of weather. The authors examined both decreasing and increasing the df to control for long-term temporal trends, matching the lags of meteorological covariates to those of the pollutants, and a squared term and moving averages of extended days (i.e., lags 0, 1–3, and 4–7) for temperature. Across all of these alternative model specifications, Kim et al. (2015) found that results were relatively consistent with the main statistical model (2.63% [95% CI: −0.22, 5.44]; lag 0–3 days unconstrained DL). Compared to Kim et al. (2015), Lee et al. (2015c) in a study of three southeastern

U.S. states and Di et al. (2017a) a national analysis only examined the sensitivity of the $PM_{2.5}$-mortality relationship to changing the df for weather covariates. Lee et al. (2015c) observed that increasing the df from 2 to 4 for the same-day temperature covariate resulted in relatively consistent risk estimates, with the percent increase in mortality ranging from 1.57 to 1.63% at lag 0–1 days. The results of Lee et al. (2015c) are consistent with those reported in Di et al. (2017a) where it was observed that increasing the natural spline df to 6 and 9 for both the temperature and dew point temperature covariates did not change the magnitude of the $PM_{2.5}$-mortality association when compared to the main analysis that used 3 df.

The recent studies focusing on short-term $PM_{2.5}$ exposures and mortality that examined alternative approaches to controlling for long-term temporal trends and the confounding effects of weather in all-year analyses are consistent with the observations from studies focusing on PM_{10} in the 2009 PM ISA. The limited assessment of model specification when conducting seasonal analyses provides some evidence that associations may be more sensitive to model specification. Overall, the results from these studies indicate that alternative approaches may influence the magnitude of the $PM_{2.5}$-mortality association, but have not been found to influence the direction of the observed association.

11.1.5.2 Influence of Long-Term $PM_{2.5}$ Concentrations on Short-Term $PM_{2.5}$ Associations

It has often been questioned whether the associations observed in epidemiologic studies of short-term air pollution exposure reflect the impact of the short-term exposure on health or are partly a reflection of exposure to air pollution over many years. This question is often posed for $PM_{2.5}$, where a large body of epidemiologic evidence demonstrates strong associations between both short- and long-term $PM_{2.5}$ exposure and mortality. In a study of the New England area, Shi et al. (2015) attempted to address the impact of different exposure durations on the $PM_{2.5}$-mortality relationship by examining both long- and short-term $PM_{2.5}$ exposures and mortality in the same statistical model. The authors observed in analyses using the full cohort that the association between short-term $PM_{2.5}$ exposure and mortality was relatively unchanged in models without adjustment (2.14% [95% CI: 1.38, 2.89]; lag 0–1) and with adjustment (2.08 [95% CI: 1.32, 2.84]) for long-term $PM_{2.5}$ exposures. These results provide additional evidence confirming the relationship between short-term $PM_{2.5}$ exposure and mortality.

11.1.6 Effect Modification of the $PM_{2.5}$-Mortality Relationship

The examination of effect modification of the $PM_{2.5}$-mortality relationship can be divided into several categories. There are some studies that examine whether specific individual- or population-level characteristics modify the $PM_{2.5}$-mortality association, which can provide information pertaining to whether certain populations are at increased risk of a PM-related health effect. Other studies focus more

broadly on examining those factors that potentially modify that $PM_{2.5}$-mortality association, and may explain some of the observed geographic heterogeneity in risk estimates. A detailed discussion of populations potentially at increased risk of PM-related health effects can be found in Chapter 12. As a result, this subsection focuses on exploring those factors that may modify the $PM_{2.5}$-mortality association and provide insight on the heterogeneity in risk estimates.

11.1.6.1 Season

The examination of whether $PM_{2.5}$-mortality associations differ by season can provide a better understanding of the overall relationship between short-term $PM_{2.5}$ exposure and mortality. The 2009 PM ISA reported some evidence that $PM_{2.5}$-mortality associations are larger in magnitude during the warm season, specifically the spring, with the majority of this evidence coming from U.S. multicity studies (Zanobetti and Schwartz, 2009; Franklin et al., 2008). Recent multicity studies generally support the seasonal patterns of associations previously observed, and due to the larger sample size allow for a more robust evaluation of potential seasonal differences.

Among the recent U.S.-based multicity studies, Dai et al. (2014) observed a larger risk during the spring with a 2.9% (95% CI: 2.2, 3.5%) increase in total (nonaccidental) mortality at lag 0–1, but positive associations were observed across the summer, fall, and winter ranging from 0.46–1.2%. Although the magnitude of the association was larger in Dai et al. (2014), in the NPACT study, Lippmann et al. (2013a) observed a larger $PM_{2.5}$-mortality effect in the warm season (April–September) (0.35% [95% CI: 0.13, 0.58%]; lag 0) and evidence of no association in the cold season among 148 U.S. cities. Interestingly, Krall et al. (2013) observed no evidence of seasonal differences in $PM_{2.5}$-mortality associations across 72 U.S. cities, which included the same study years as Dai et al. (2014) and Lippmann et al. (2013a). Although some study design aspects differ among the studies, the overall design of Krall et al. (2013) and Lippmann et al. (2013a) are similar as are the underlying statistical models, which further complicates the interpretation of the disparate results with respect to seasonal associations between the studies. However, each of the studies reported positive associations in all-year analyses even though the magnitude varied (Figure 11-1).

European multicity studies support the results observed in Dai et al. (2014) and Lippmann et al. (2013a) of associations larger in magnitude during warmer months of the year. In a study of 20 European Mediterranean cities, Samoli et al. (2013) observed larger associations during the warm season (2.2% [95% CI: 1.5, 3.0]; lag 0–1) compared to the cold season (0.23% [95% CI: −0.08, 0.54]). Pascal et al. (2014) also observed larger associations during the summer (3.4% [95% CI: 1.8, 5.1]; lag 0–1) compared to the other three seasons with estimates ranging from −0.6 to 0.9%. However, in copollutant models with O_3 the authors observed that associations across all seasons persisted, except the summer (0.50% [95% CI: −3.3, 4.4]) indicating some evidence of potential confounding by O_3.

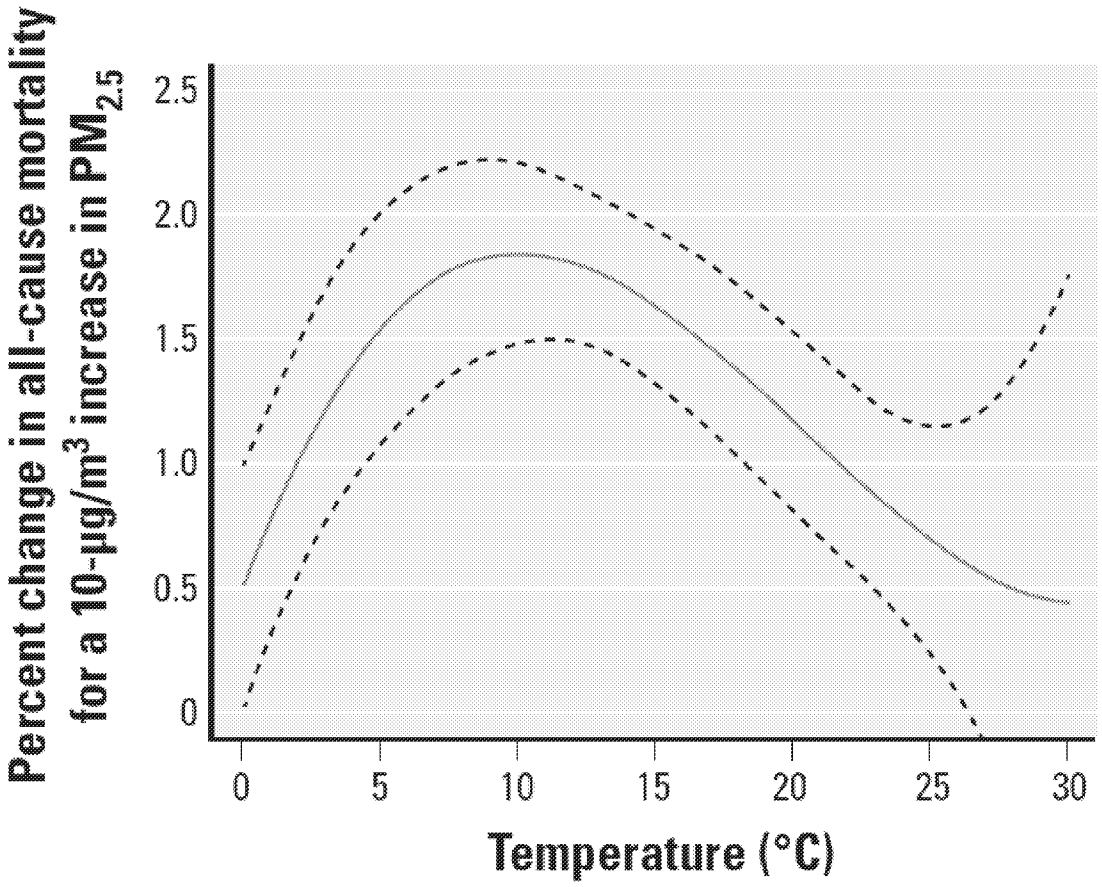
Across recent multicity studies, there was general agreement that $PM_{2.5}$-mortality associations were larger in magnitude during warmer months. However, it remains unclear if copollutants confound the seasonal patterns in associations observed. Across most studies the pattern of seasonal associations persisted using different methods to examine whether there was evidence of seasonal differences in associations with some studies relying on stratified analyses (Dai et al., 2014; Samoli et al., 2013) and others incorporating interaction terms between $PM_{2.5}$ and season (Pascal et al., 2014; Lippmann et al., 2013a).

11.1.6.2 Temperature

Seasonal analyses, such as those discussed above, indirectly take into consideration the role of temperature on the $PM_{2.5}$-mortality association. However, these studies do not directly address the question of whether higher or lower temperature days modify the $PM_{2.5}$-mortality association. Studies by Dai et al. (2014) and Pascal et al. (2014) further explore the role of temperature on the $PM_{2.5}$-mortality relationship.

Previous studies have demonstrated an inverted U-shape curve between temperature and indoor ventilation, which potentially influences exposure to $PM_{2.5}$ (Koutrakis et al., 2005). In a study of 75 U.S. cities, Dai et al. (2014) examined the influence of city-season mean temperature on the $PM_{2.5}$-mortality association. Consistent with the observations of Koutrakis et al. (2005) the authors found a smaller $PM_{2.5}$-mortality association during high and low temperatures, which could be attributed to reduced indoor penetration of $PM_{2.5}$ as a result of less ventilation (Figure 11-5).

Whereas Dai et al. (2014) focused on examining the $PM_{2.5}$-mortality relationship across the distribution of city-season temperatures, Pascal et al. (2014) focused on the "extra effect of PM during warm days." The authors defined warm days as those days "when the mean temperature equals or exceeds the 97.5th percentile of the mean temperature distribution" (Pascal et al., 2014). Stratifying on days above the 97.5th percentile, Pascal et al. (2014) reported a larger increase in nonaccidental mortality on warm days (1.4% [95% CI: −5.5, 8.9]; lag 0−1) compared to nonwarm days (0.70% [95% CI: −0.10, 1.5]); however, confidence intervals were large indicating a small number of days with temperatures within this range of the temperature distribution. The interaction term examining the additional PM-mortality effect attributed to high temperatures was similar to the warm days stratified result, i.e., indicating potential evidence of effect measure modification, but with wide confidence intervals (interaction ratio: 1.03 [95% CI: 0.97, 1.11]).



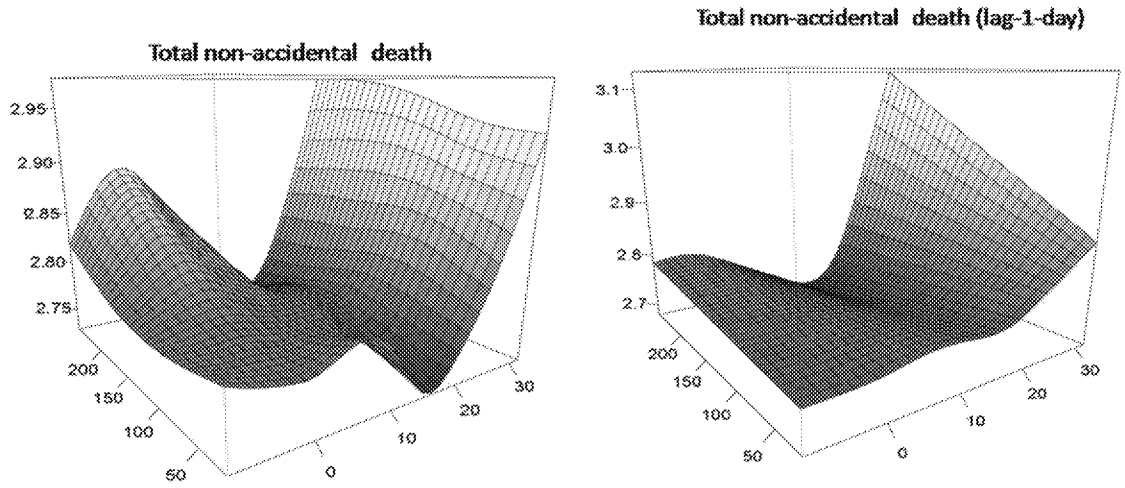
Source: Permission pending, Dai et al. (2014).

Figure 11-5 Relationship between estimated $PM_{2.5}$-mortality association and temperature.

Additional studies conducted by Sun et al. (2015) and Li et al. (2015), in Hong Kong and Beijing, respectively, had mean $PM_{2.5}$ concentrations over 20 μg/m^3 during the study duration, but used unique approaches to examine the potential interactive effect of temperature on the $PM_{2.5}$-mortality relationship. Sun et al. (2015) first identified the lag structure over which there was evidence of a temperature-mortality relationship for both cold and warm temperatures using generalized cross-validation (GCV). This process identified a 0−6-day lag for cold temperatures and a 0−1-day lag for warm temperatures. The authors then defined the cold and warm temperature cutoff by identifying the temperature at which the log relative risk of the temperature-mortality relationship was equal to zero resulting in low temperatures being defined as <22°C, medium temperatures as 22–25°C, and high temperatures as ≥25° C. In a stratified analysis, Sun et al. (2015) reported evidence of a larger association for $PM_{2.5}$ and total (nonaccidental) mortality in Hong Kong for lower temperatures (0.94% [95% CI: 0.65,

1.2]; lag 0−1) when compared to higher temperatures (0.47% [95% CI: 0.18, 0.76]). This pattern of associations persisted in copollutant models with NO_2, SO_2, and O_3.

A different pattern of $PM_{2.5}$-mortality associations was observed by Li et al. (2015) when examining the influence of temperature. The authors first visually examined the combined effects of temperature and $PM_{2.5}$ on mortality using a nonparametric bivariate response surface. Using the results of the bivariate model allowed for the identification of temperature ranges that could be examined by conducting a stratification analysis (i.e., low temperature <2.6°C, medium temperature 2.6–23.5°C, and high temperature >23.5°C). Whereas Sun et al. (2015) observed larger mortality associations only at higher temperatures, in the bivariate response model Li et al. (2015) reported evidence of larger $PM_{2.5}$-mortality associations at both low and high temperatures, specifically at lag 0 (Figure 11-6). However, it is important to note that the definition of low temperature for Li et al. (2015) and Sun et al. (2015) differed, complicating the comparison of results between these two studies.



Note: *y*-axis = percent increase in mortality, *z*-axis = $PM_{2.5}$ concentrations, and *x*-axis = temperature (°C).
Source: Permission pending, Li et al. (2015).

Figure 11-6 Bivariate $PM_{2.5}$-temperature response surfaces for total (nonaccidental) mortality using same-day 24-hour mean temperature and lag 0 and lag 1 $PM_{2.5}$ concentrations.

The observation from the bivariate model was confirmed when examining $PM_{2.5}$-mortality associations at the various temperature ranges in the stratified analysis. The magnitude of the association was similar at both the low and high temperatures at both lag 0 (low temperature: 1.3 [95% CI: 0.46, 2.0]; high temperature: 1.4 [95% CI: 0.35, 2.4]) and lag 1 (low temperature: 1.1 [95% CI: 0.48, 1.7]; high temperature: 1.1 [95% CI: 0.76, 2.1]).

Overall, the examination of the potential modification of the $PM_{2.5}$-mortality relationship by temperature remains unclear. Although there is some evidence of an increase in the magnitude of the $PM_{2.5}$ association at both lower and higher temperatures in studies conducted at higher $PM_{2.5}$ concentrations, to date studies conducted within the U.S. have not provided evidence of a modification of the $PM_{2.5}$-mortality association by temperature.

11.1.6.3 City and Regional Characteristics

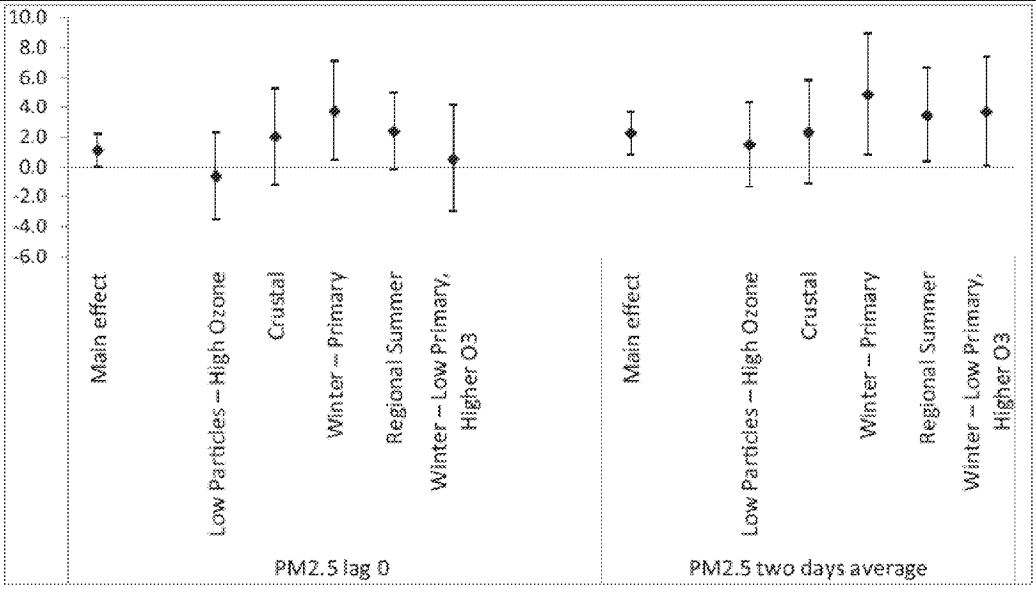
It has often been hypothesized the heterogeneity in $PM_{2.5}$-mortality associations observed across cities could be attributed to city-specific differences in population demographics, $PM_{2.5}$ composition, or exposure characteristics. Studies of population demographics often focus on whether there is evidence of effect modification and not on how risk may change between cities due to demographic differences. In the 2009 PM ISA, the evaluation of the observed heterogeneity in $PM_{2.5}$-mortality associations was limited to studies examining whether individual $PM_{2.5}$ components or the prevalence of air conditioning use, a surrogate for decreased PM penetration indoors, modified the association. Although examining the modification of the PM-mortality relationship by $PM_{2.5}$ components included studies focusing on PM_{10}, overall a number of components were found to potentially explain the city-to-city heterogeneity (U.S. EPA, 2009). Additionally, there was some evidence that the prevalence of air conditioning (AC) use across cities modifies the $PM_{2.5}$-mortality association and that $PM_{2.5}$-mortality associations vary by region of the country (i.e., east vs. west) (U.S. EPA, 2009). Although $PM_{2.5}$ composition, AC use, and geographic location may explain some of the heterogeneity in $PM_{2.5}$-mortality risk estimates, at the completion of the 2009 PM ISA it remained unclear what factors or combination of factors explain the observed heterogeneity. Recent studies discussed in the following sections have expanded upon the initial analyses detailed in the 2009 PM ISA by examining whether specific $PM_{2.5}$ components/mixtures or exposure characteristics provide information that explains the heterogeneity in $PM_{2.5}$-mortality associations observed in multicity studies.

11.1.6.3.1 Composition/Mixtures

The examination of effect modification of the $PM_{2.5}$-mortality association, by either an individual $PM_{2.5}$ component or the proportion of a $PM_{2.5}$ component to mass, is one of the traditional approaches that has been employed to examine the influence of PM composition on the $PM_{2.5}$-mortality relationship. Although detailed as one of the main approaches used to examine the association between a $PM_{2.5}$ component and a health outcome in Mostofsky et al. (2012), these studies are discussed within this section because they have primarily been used as a means to explain the heterogeneity in $PM_{2.5}$-mortality risk estimates observed between cities or regions of a country. Other studies focusing specifically on examining the effect of individual $PM_{2.5}$ components on mortality are detailed in Section 11.1.11.

As part of the NPACT study and in a study of 75 U.S. cities, Lippmann et al. (2013a) and Dai et al. (2014) conducted analyses similar to those in Franklin et al. (2008), which was evaluated in the 2009 PM ISA, to examine whether specific pollutants modify the $PM_{2.5}$-mortality relationship. Lippmann et al. (2013a) examined the modifying effect of long-term average pollutant concentrations, while Dai et al. (2014) and Franklin et al. (2008) examined the $PM_{2.5}$ component to $PM_{2.5}$ mass proportion. In a second-stage analysis, Lippmann et al. (2013a) reported evidence that as the IQR of mean concentrations of pollutants increased across cities, the $PM_{2.5}$-mortality association increased in magnitude, specifically with SO_4^{2-}, weekday excess $PM_{2.5}$, Pb, and V. There was additional evidence that other pollutants (e.g., Cu, Se) may also contribute to modifying the $PM_{2.5}$-mortality association, but to a lesser extent, as was evident by the wider confidence intervals. Dai et al. (2014) used the monthly component-to-$PM_{2.5}$ proportion in the second-stage analysis to examine effect modification and observed as the distribution of the proportion increased from the 10th to 90th percentile there was evidence of larger $PM_{2.5}$-mortality associations for Si, S, and Ca. Although Dai et al. (2014) and Lippmann et al. (2013a) did not report consistent results, Lippmann et al. (2013a) and Franklin et al. (2008) both reported some evidence that SO_4^{2-} potentially increases the magnitude of the $PM_{2.5}$-mortality relationship and may explain some of the heterogeneity in risk estimates.

In addition to the traditional effect modification approaches to examining heterogeneity, such as those used in Lippmann et al. (2013a) and Dai et al. (2014), a number of recent studies have explored alternative, and to an extent more novel approaches such as whether cities have unique pollution profiles, to examine if city or region specific pollutant characteristics help explain differences in $PM_{2.5}$-mortality risk estimates observed between cities and regions within the U.S. One such approach developed by Zanobetti et al. (2014a) explores whether distinct daily pollution profiles modify the $PM_{2.5}$-mortality relationship, and although limited to Boston, MA, could be applicable to examining heterogeneity between cities or regions. The authors used $PM_{2.5}$ component data along with gaseous pollutant data from 1999–2009 to identify five distinct pollution profiles through the use of *k*-means clustering, which was detailed in Austin et al. (2012). The five clusters identified were representative of days with low particles—high O_3; crustal; winter—primary; regional summer; and winter—low primary, higher O_3. In single-pollutant models with $PM_{2.5}$, the authors observed a 1.1% increase in mortality (95% CI: 0.0, 2.2) at lag 0 and a 2.3 % increase (95% CI: 0.9, 3.7) at lag 0–1. When examining whether days with specific pollution profiles modified the $PM_{2.5}$-mortality relationship, Zanobetti et al. (2014a) reported evidence that at lag 0 the winter—primary cluster, which has a strong contribution from traffic and oil combustion, had the largest effect, with some evidence that the crustal and regional summer clusters modified the association. A similar pattern of results was observed when examining lag 0–1, but with the magnitude of the association slightly larger for each pollution profile (Figure 11-7). Overall, this study indicates that specific pollution profiles may modify the $PM_{2.5}$-mortality relationship.

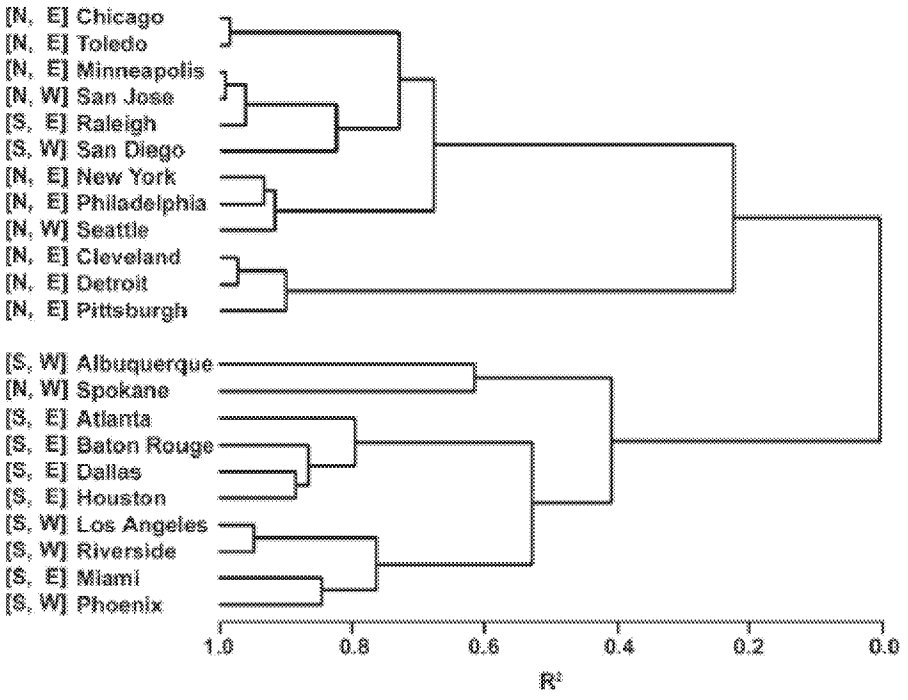


Source: Permission pending, Zanobetti et al. (2014a).

Figure 11-7 Percent increase in mortality for a 10 μg/m^3 increase in $PM_{2.5}$ concentrations at lag 0 and lag 0–1 in single-pollutant models and models containing indicator variables representative of days with specific pollution profiles.

Davis et al. (2011) approached the question of heterogeneity in $PM_{2.5}$-mortality risk estimates using a more qualitative approach. Specifically, the authors focused on whether there was evidence of broad regional patterns in $PM_{2.5}$ component concentrations by examining if groups of cities have similar $PM_{2.5}$ component profiles and if there are regional differences in individual $PM_{2.5}$ component concentrations. To conduct this analysis the authors focused on the 30 cities within the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) that represented the 20 most populated cities and 10 midsize cities that were selected to provide regional coverage across the U.S. Data for 20 $PM_{2.5}$ components from the CSN for the years 2005–2007. Of the cities included in the study, only 17 large and 5 midsize cities had sufficient monitoring data to be included in the cluster analysis. After normalizing the data across cities by calculating the coefficient of divergence (COD) between data sets in each city, a hierarchical cluster analysis was used to group cities with similarities in $PM_{2.5}$ component concentrations. Based on the clustering analysis there was evidence of a north-south delineation in cities with similar $PM_{2.5}$ component concentrations, with the exception of three cities (i.e., Raleigh, San Diego, and Spokane), and not the east-west delineation that has often been observed when examining geographic differences in $PM_{2.5}$-mortality risk estimates as detailed in the 2009 PM ISA (U.S. EPA, 2009) (Figure 11-8). This potential north-south delineation was further reflected when examining whether there are regional differences in individual $PM_{2.5}$ component concentrations using the Wilcoxon two-sample test. In east-west analyses, crustal components (e.g., Al, Si, Ti, Fe, and K) and nitrate were found to be higher in

the West, whereas higher sulfur was observed in the East. There was no evidence of east-west differences in combustion-related components. However, when examining north-south contrasts there was evidence of higher concentrations of combustion-related components, sulfate and nitrate in the North and crustal components and OC in the South. Collectively these results support regional differences in the composition of $PM_{2.5}$. However, within geographic regions there is city-to-city heterogeneity in $PM_{2.5}$ mortality risk estimates, which complicates the interpretation of the regional pattern of associations observed in studies such as Davis et al. (2011).



Note: N = north, S = south, W = west, E = east.
Source: Permission pending, Davis et al. (2011).

Figure 11-8 Dendrogram showing relationships among the 17 largest and 5 midsize National Morbidity, Mortality, and Air Pollution Study (NMMAPS) cities using $PM_{2.5}$ composition data from Chemical Speciation Network (CSN) for 2005–2007.

While Davis et al. (2011) focused on broad regional differences in the composition of $PM_{2.5}$ and its potential role in explaining the heterogeneity in $PM_{2.5}$-mortality risk estimates, Baxter et al. (2013) focused specifically in trying to identify potential contributors to the city-to-city differences in risk estimates observed in multicity epidemiologic studies. Baxter et al. (2013) conducted a semiquantitative analysis focusing on $PM_{2.5}$ component and gaseous pollutant concentrations to gain a better understanding

of their relationship with $PM_{2.5}$ mass, and their potential influence on $PM_{2.5}$-mortality risk estimates. Focusing on the results from a study of 27 U.S. cities conducted by Franklin et al. (2007), Baxter et al. (2013) explored city-specific air pollution characteristics for the two cities in each region of the U.S. with the largest and smallest $PM_{2.5}$-mortality risk estimates (i.e., Northeast: Boston, MA [largest] and Pittsburgh, PA; South: Memphis, TN [largest] and Birmingham, AL; Midwest: Milwaukee, WI [largest] and Detroit, MI; West: San Diego, CA [largest] and Riverside, CA). To explore air pollution characteristics of each city, the authors examined (1) percent contribution of each $PM_{2.5}$ component to $PM_{2.5}$ mass; (2 and 3) Spearman correlation and COD between each city pair and pollutant (21 $PM_{2.5}$ components, $PM_{2.5}$ mass, and gaseous pollutants); (4) Spearman correlation between each $PM_{2.5}$ component and gaseous pollutant and $PM_{2.5}$ mass in each city; and (5) composition of air pollution mixtures in each city to identify whether sources differ between cities by conducting a principal component analysis (PCA) including both PM and gaseous pollutant data. Although there were some differences between cities, this analysis did not identify one component or group of components that could explain the difference between city pairs. Additionally, in the source-based analysis, differences were observed between cities when focusing on local sources such as motor vehicle and industry, but one or more sources were not identified that could explain the difference in risk estimates between cities. Overall, the study by Baxter et al. (2013) indicates some differences in $PM_{2.5}$ composition and sources between cities, but also demonstrates that city-to-city differences in $PM_{2.5}$-mortality risk estimates are not limited to $PM_{2.5}$ source and composition differences.

11.1.6.3.2 Exposure Factors

Many studies that have examined heterogeneity in $PM_{2.5}$-mortality risk estimates often examine whether specific city characteristics modify the association. This examination occurs in a second-stage analysis that focuses on the distribution of a factor (e.g., percentage poverty) across cities and how risk changes moving from the low end to the high end of the distribution. Lippmann et al. (2013a) used this more traditional approach, but focused on a suite of city-specific variables (i.e., land-use, port-, and traffic-related data) that could reflect exposure differences. The evidence indicated that port berth volume within 60 miles of a city along with the sum of road lengths within a city increased the risk of $PM_{2.5}$-related mortality. There was also evidence that percent of a city developed and percent of a city with wetland positively increased risk, but with greater uncertainty. The relationship between $PM_{2.5}$-mortality risk and port berth volume is supported by the negative relationship with distance to large port. The results of Lippmann et al. (2013a) provides evidence that city-specific factors that may influence exposure can influence the $PM_{2.5}$-mortality relationship across cities.

Unlike Lippmann et al. (2013a) where the focus was on community-level factors that may modify the $PM_{2.5}$-mortality relationship, Baxter and Sacks (2014), which in some respect is an expansion of Baxter et al. (2013), focused on exploring whether there are city-specific exposure profiles that may have a role in explaining the observed heterogeneity. Using data from the American Housing Survey (AHS) for

94 Core-Based Statistical Areas (CBSAs) with a population greater than 500,000 from 2001–2005, the authors used k-means clustering to examine whether there were unique CBSA clusters based on residential infiltration factors (i.e., percent of homes with central AC, mean year home was built, and mean home size) and both residential infiltration factors and commuting factors (i.e., mean in-vehicle commuting time and mean in-vehicle commuting distance). The residential infiltration factor analysis identified five clusters, with a large number of the cities in clusters 1 (N = 24) and 3 (N = 40). The main difference between these clusters were the mean home age was slightly older for cluster 1, while there was a greater percent of central AC in cluster 3. There was evidence of a geographic pattern in the clustering of cities as reflected in Figure 11-9. The combination of residential infiltration and commuting factors resulted in the identification of 10 clusters. Across clusters, only two clusters had more than 11 CBSAs, clusters 8 and 9, which primarily differed by percent of homes with central AC. Cities with shorter commuting times were found to also have shorter commuting distances. Although not as pronounced as the residential infiltration analysis there tended to be a geographic pattern in the residential infiltration and commuting factor analysis (Figure 11-9). In Baxter and Sacks (2014) 66 of the CBSAs encompassed cities included in NMMAPS, therefore, the cluster analysis results were compared to city-specific PM_{10}-mortality risk estimates from NMMAPS. Recognizing the potential differences in infiltration between $PM_{2.5}$ and PM_{10}, given that $PM_{2.5}$ comprises varying proportions of PM_{10}, the results provide some evidence that cities with older homes and a smaller percent of central AC have higher risk estimates compared to cities with newer homes and a larger percent of central AC. Although the addition of commuting factors to the cluster analysis could reveal some additional exposure nuances between cities, the small number of CBSAs in each cluster complicates the interpretation of the combined analyses. Overall, the results of Baxter and Sacks (2014) provide initial evidence that certain differences in exposure characteristics between cities may also contribute to explaining the city-to-city heterogeneity in $PM_{2.5}$-mortality risk estimates.

Source: Permission pending, Baxter and Sacks (2014).

Figure 11-9 Maps of Core-Based Statistical Areas (CBSAs) by cluster based on (A) residential infiltration factors and (B) residential infiltration and commuting factors.

Baxter et al. (2017) built off the cluster analysis detailed in Baxter and Sacks (2014), and used only the residential infiltration-based clusters as a means to explore whether there are differences in the $PM_{2.5}$-mortality association across clusters and if the clusters explain the observed heterogeneity. In the analysis, 77 U.S. cities were grouped into five clusters based on prevalence of central air conditioning, mean year home was built, and mean size of home. Focusing on those clusters where the number of cities included was greater than 5, there is some evidence of differences in $PM_{2.5}$ mortality risk estimates that could be attributed to differential exposure as a result of residential infiltration. For example, clusters 1 and 3 were representative of smaller homes, but with differing age and percent of air conditioning. Cluster 3 homes had a higher percentage of central air conditioning and were newer than cluster 1, but the risk estimates in both clusters were the smallest across clusters (cluster 1: −0.01% [95% CI: −0.31, 0.29]; cluster 3: 0.25 [95% CI: −0.15, 0.65]). Cluster 4, which was representative of larger homes that were older with a moderate percentage of central air conditioning (i.e., 55.7%) had the largest risk estimate (0.66% [95% CI: 0.35, 0.97]). These results are consistent with previous studies that have demonstrated that air exchange rates are higher in larger and older homes, resulting in increased exposures to ambient

PM (Section 3.4.1.1). In a second-stage analysis, the authors further examined the role of the clusters in explaining the observed heterogeneity and whether the individual residential infiltration factors alone contributed to the heterogeneity. Baxter et al. (2017) reported that cluster assignment explained 6% of the observed heterogeneity, and that only larger home size modified the $PM_{2.5}$-mortality association, which is consistent with the results of the main cluster analysis.

11.1.7 Evaluation of Exposure Assessment Techniques

As described in the previous section, a number of factors have been considered in an attempt to explain the heterogeneity in $PM_{2.5}$-mortality risk estimates. An underlying factor not discussed in the previous section is the potential role of exposure assessment and exposure misclassification (see Section 3.4.2). Traditionally, air pollution epidemiology studies have relied upon single monitors or the average of multiple monitors over some geographic extent (e.g., county) to assign exposure. Recent studies have examined the influence of distance to monitor on the $PM_{2.5}$-mortality association. Additionally, new and innovative approaches have been developed that use ensemble approaches to combine air pollution data from a number of sources including ambient monitors and satellite data, as well as model predictions in an attempt to obtain a more refined estimate of exposure. The following section discusses these approaches and how this information further informs the $PM_{2.5}$-mortality relationship.

11.1.7.1 Monitor Representativeness

Recent studies by Davis et al. (2011), Kloog et al. (2013), Kim et al. (2015), and Di et al. (2017a) conducted sensitivity analyses to examine the potential influence of distance to monitor on the relationship between short-term $PM_{2.5}$ exposure and mortality. These types of analyses can provide information on exposure assessment that may influence the city-to-city or regional heterogeneity observed in multicity epidemiologic studies.

As part of their analysis examining if there are broad $PM_{2.5}$ composition differences between regions, Davis et al. (2011) also explored the representativeness of ambient monitors to reflect population exposure. Both on an individual city level as well as the broad regional classifications identified (i.e., north versus south, and east versus west), the authors examined the percent of the population residing within 1 km, 5 km, 10 km, and 15 km from an AQS monitor. Less than 50% of the population across almost all cities resided within 5 km of a monitor. Interestingly, of the 20 cities with populations over 1 million people, almost half of the cities had up to 20% of the population residing greater than 15 km of an AQS monitor. In the regional designations, a larger percent of people was closer to monitors at all distances for both the East and North designations. The 2009 PM ISA (U.S. EPA, 2009) presented data for intermonitor correlation versus distance between monitors to examine the influence of distance to

monitor on exposure assessment (see Section 3.4.2.2). Correlations of approximately Pearson $R = 0.90$ were reported for intermonitor distances of 15 km in three cities (Boston, Pittsburgh, and Los Angeles) with correlations largely above 0.8 at distances of 50 km in Boston in Pittsburgh. These findings indicate that temporal variability of $PM_{2.5}$ concentrations are often similar over urban scales. Therefore, large errors in the exposure time-series are not anticipated across large distances for the cities included in Davis et al. (2011).

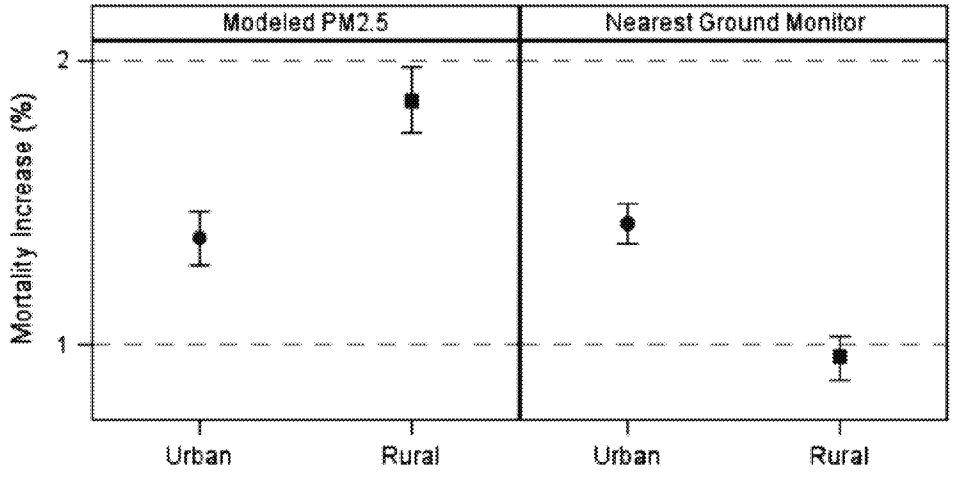
Recent studies examined the influence of distance to monitor on the association between short-term $PM_{2.5}$ exposure and mortality. Kloog et al. (2013) examined the impact of distance to monitor on the daily $PM_{2.5}$-mortality association as part of a study conducted in Massachusetts. Within this study, daily $PM_{2.5}$ concentrations were predicted to 10 × 10 km grid cells using satellite data that were calibrated with ground-level $PM_{2.5}$ measurements. Additionally, land-use regression and weather variables were used to predict $PM_{2.5}$ concentrations on days where AOD values were not available. In a sensitivity analysis, the authors examined associations based on distance to monitor, defined as greater than or less than 20 km from an ambient monitor. In models that included an interaction term for distance to monitor, Kloog et al. (2013) reported a 4.5% increase in mortality (95% CI: 2.6, 6.5) near a monitor and 1.4% increase in mortality (95% CI: 0.8, 2.0) far from a monitor at lag 0−1, compared with a 2.8% increase in mortality (95% CI: 2.0,3.5) across the study population. Di et al. (2017a) also conducted a sensitivity analysis examining $PM_{2.5}$-mortality associations based on the nearest monitor within 50 km. In the main analysis, the authors predicted $PM_{2.5}$ and O_3 concentrations to 1 km × 1 km grid cells based on the combination of ambient monitoring data, satellite measurements, land-use data, and chemical transport modeling. $PM_{2.5}$ exposures were assigned to the zip code level and in a model that adjusted for O_3, Di et al. (2017a) reported a 1.05% increase (95% CI: 0.95, 1.15) in all-cause mortality at lag 0−1 days within the Medicare population. In the nearest monitor analysis, the authors also reported a positive association, but it was smaller in magnitude (0.83% [95% CI: 0.73, 0.93]; lag 0−1), which is consistent with the results of Kloog et al. (2013) and indicative of some degree of exposure misclassification at distances further from monitors. However, Kim et al. (2015) as part of the DASH study in Denver, CO, examined the $PM_{2.5}$-mortality association at 10 km and 20 km buffers around a single monitor and found no evidence of a difference in the association across buffers. As discussed in Davis et al. (2011) and in Section 2.5.1.2.1 this could reflect the spatial and temporal characteristics of $PM_{2.5}$ in Denver, which may differ from those observed in Kloog et al. (2013) in Massachusetts and Di et al. (2017a) nationally.

11.1.7.2 Urban versus Rural Locations

As detailed in Chapter 3, new and innovative statistical approaches have been developed to obtain more refined exposure estimates, particularly in areas that do not have ambient monitors (i.e., rural locations). The studies by Kloog et al. (2013), Shi et al. (2015), and Lee et al. (2015c) all employed some derivation of a similar approach to estimate $PM_{2.5}$ concentrations that relied upon satellite measurements.

The question that often arises from studies such as these is: How well does the method employed capture $PM_{2.5}$ concentrations in areas that do not have monitors?

Of the studies conducted to date, only Lee et al. (2015c) explored the difference between urban and rural $PM_{2.5}$-mortality associations using both the modeled data, which incorporated satellite measurements, and the nearest ambient monitor across three southeastern U.S. states. Using the modeled $PM_{2.5}$ data, the authors reported evidence of a larger association in rural compared to urban locations, but when assigning exposure using data from ambient $PM_{2.5}$ monitors, the rural location association remained positive although it was attenuated (Figure 11-10). Overall, the results from Lee et al. (2015c) provide some evidence for potential differences in $PM_{2.5}$-mortality associations between urban and rural locations, but uncertainties remain due to the relative sparseness of monitors in rural locations and the known differences in $PM_{2.5}$ sources between locations.



Source: Permission pending, Lee et al. (2015c).

Figure 11-10 Percent increase in mortality at lag 0–1 for a 10 µg/m³ increase in 24-hour average $PM_{2.5}$ concentrations based on location of residence using modeled and monitored $PM_{2.5}$ concentrations.

11.1.8 Timing of Effects and Exposure Metrics

11.1.8.1 Lag Structure of Associations

Within the 2009 PM ISA, the studies evaluated indicated that the effect of short-term $PM_{2.5}$ exposure on mortality was immediate, occurring within the first few days after exposure, with the strongest evidence, in terms of magnitude and precision of the associations, in the range of 0 to 1 day.

However, these studies defined the lags to examine a priori and often in accordance with the 1-in-3 or 1-in-6 day sampling schedule of ambient $PM_{2.5}$ monitors. Additionally, these mortality studies examined associations with $PM_{2.5}$ using a 24-hour average exposure metric, resulting in the inability to determine whether subdaily exposure metrics (e.g., 1-hour max) capture other exposures of concern. Some studies published since the completion of the 2009 PM ISA have conducted more extensive examinations of the lag structure of associations for short-term $PM_{2.5}$ exposures and mortality, focused on subdaily exposure metrics to understand the role of peak $PM_{2.5}$ concentrations on the $PM_{2.5}$-mortality relationship, and examined whether the risk of mortality attributed to short-term $PM_{2.5}$ exposure has changed over time.

The studies evaluated in the 2009 PM ISA did not conduct a systematic evaluation of the lag structure of associations between short-term $PM_{2.5}$ exposure and mortality, but reported evidence of consistent, positive associations within the first few days after exposure (i.e., 0−1 lag days) (U.S. EPA, 2009). Recent studies have conducted analyses aimed at understanding the timing of effects between short-term $PM_{2.5}$ exposure and mortality. Studies have ranged in their level of evaluation from examining multiple individual or multiday lags to more systematically examining whether there is evidence of immediate (e.g., lag 0−1 days), delayed (e.g., lag 2−5 days), or prolonged (e.g., lag 0−5 days) effects. However, a number of studies do not provide the information necessary to systematically evaluate the timing of the relationship between $PM_{2.5}$ exposure and mortality. For example, in a study conducted in the Netherlands, Janssen et al. (2013) examined single-day lags ranging from 0 to 3 days, along with the inclusion of a lag encompassing the average of 0−6 days. By not including information on lag days 4, 5, and 6 only the single-day lag information can be interpreted because it is not possible to differentiate whether considering a longer lag is reasonable.

The evidence from experimental studies can provide information on the biological plausibility of the timing between exposure and effect. In the case of cardiovascular mortality, which encompasses ~33% of total (nonaccidental) mortality (NHLBI, 2017), it is well characterized that short-term $PM_{2.5}$ exposure results in rather immediate cardiovascular responses (Section 6.1.14.3), providing biological plausibility for the focus of most $PM_{2.5}$-mortality studies on shorter windows of exposure, in the range of 0 to 2 days. However, the evidence for a respiratory effect in response to short-term $PM_{2.5}$ exposure has been found to be more delayed, which provides biological plausibility for examining associations with respiratory mortality at longer lags (Section 5.1.10.3). Although the discussion of lag structure of associations for cause-specific mortality will be detailed in the respective cardiovascular and respiratory chapters, the biological plausibility of the timing of effects for cardiovascular and respiratory mortality provide the basis for focusing the discussion on the lag structure of associations on those studies that: evaluate a series of single-day lags (e.g., lags 0 to 3 days); conduct a systematic evaluation of different lags (e.g., single-day versus distributed or average of multiple days); and include all single days evaluated in the distributed or multiday average lags (i.e., if a study examines a distributed or multiday average lag of 0−6 days it also examines single-day lags of 0 to 6 days).

Most of the recent studies that examined the lag structure of associations for the $PM_{2.5}$-mortality relationship either conducted analyses of single-day lags over multiple days or various iterations of multiday lags (e.g., 0–1, 0–2, 0–3, etc.). As part of the NPACT study, Lippmann et al. (2013b) examined single-day lags ranging from 0 to 3 days. In all-year analyses, the strongest associations, in terms of magnitude and precision, with total (nonaccidental) mortality were at lags 0 and 1 day, with associations persisting in the warm season and no evidence of an association in the cold season. The results of Lippmann et al. (2013b) are consistent with the pattern of associations observed in other multicity studies that also examined a series of single-day lags (Di et al., 2017a; Stafoggia et al., 2017; Janssen et al., 2013). Di et al. (2017a) examined single-day lags of 0 to 4 days and compared these results to the main analysis that used a multiday lag of 0–1 days. It is important to note that the main analysis as well as these sensitivity analyses were based on a model that also adjusted for O_3. Across the single-day lags, results support an immediate effect as reflected by largest magnitude of an association for lag 0 and 1 day (~ 0.75% increase in all-cause mortality), but these associations were smaller in magnitude to the main analysis that used the multiday lag of 0–1 days (1.05% [95% CI: 0.95, 1.15]). When examining the other single-day lags, Di et al. (2017a) reported a much smaller association at lag 2 (~0.25% increase), with no evidence of an association at lag 3 and 4. In an examination of single-day lags (i.e., 0 to 3 days), Janssen et al. (2013) reported rather immediate effects with associations similar in magnitude (0.8–1.0%) across each of the single-day lags. An examination of single-day lags ranging from 0 to 10 days in a study of eight European cities reported the strongest association at lag 1 (Stafoggia et al., 2017). The pattern of associations observed across studies that examined a series of single-day lags is consistent with the results reported by Lee et al. (2015a) that examined a series of multiday lags and observed the strongest associations for total (nonaccidental) mortality at lag 0–1, but associations remained positive when examining multiday lags up to 0–4 days.

In the MED-PARTICLES Project, Samoli et al. (2013) conducted a systematic evaluation of the lag structure of associations by examining whether there was evidence of an immediate (lag 0–1), delayed (lag 2–5), or prolonged (lag 0–5) $PM_{2.5}$-mortality effect as well as examining the pattern of associations over lags 0 to 7 days in a polynomial distributed lag model. The authors reported a 0.55% increase in total (nonaccidental) mortality (95% CI: 0.27, 0.84) at lag 0–1, a 0.51% increase (95% CI: 0.07, 0.96) at lag 2–5, and a 0.70% increase (95% CI: 0.22, 1.18) at lag 0–5. Although the 0–5 lag shows the association largest in magnitude, the 0- to 1-day lag comprises a large amount of this effect. A closer examination of associations on a day-to-day basis through the polynomial distributed lag model shows evidence of the strongest associations within the range of 1 to 3 days (quantitative results not presented). The combination of the multi- and single-day lag analyses provides further support for the $PM_{2.5}$-mortality association being strongest within the first few days after exposure.

11.1.8.2 24-Hour Average versus Subdaily (Peak) Exposures

Most of the studies conducted to date have examined the association between short-term $PM_{2.5}$ exposure and mortality using 24-hour average exposure metrics. A few recent single-city studies examined alternative exposure metrics to further examine the relationship between short-term $PM_{2.5}$ exposure and mortality. In a study conducted in Oslo, Norway that estimated $PM_{2.5}$ concentrations using a dispersion model Madsen et al. (2012) used the traditional 24-hour average exposure metric along with one representative of peak exposures (i.e., the hourly average two daily rush hour periods; 08:00–10:00 and 15:00–17:00). Within this study mean peak concentrations were approximately 23 $\mu g/m^3$, while 24-hour average concentrations were 15.1 $\mu g/m^3$. The authors observed the same pattern of associations across the single and multiday lags examined (i.e., lags 4 and 5, and 0−4 and 0−5 days) for the 24-hour average and peak exposure metric with the magnitude being slightly larger for the 24-hour average metric (quantitative results not provided). Although Lin et al. (2016) examined peak and 24-hour average $PM_{2.5}$ exposures that were much higher (i.e., 1-hour max = 66.9 $\mu g/m^3$ and 24-hour average = 46.4 $\mu g/m^3$) than those reported in Madsen et al. (2012), the results from this study can further inform our understanding of alternative exposure metrics. Unlike Madsen et al. (2012) which used $PM_{2.5}$ concentrations predicted from a dispersion model, $PM_{2.5}$ concentrations in Lin et al. (2016) were measured over 11 ambient monitors throughout Guangzhou, China. In analyses of peak and 24-hour average $PM_{2.5}$ exposures and cardiovascular mortality at single day lags ranging from 0 to 5 days, and multiday lags from 0 to 3 days, the authors observed a consistent pattern of associations across lags for both exposure metrics, with the magnitude of the association often larger in models with the 24-hour average metric. The results of Lin et al. (2016) are consistent with those observed in Madsen et al. (2012), which collectively provide initial evidence that when comparing subdaily and 24-hour average exposure metrics, the 24-hour average exposure metric is consistently associated with mortality.

11.1.9 Alternative PM Size Fractions and Exposure Metrics

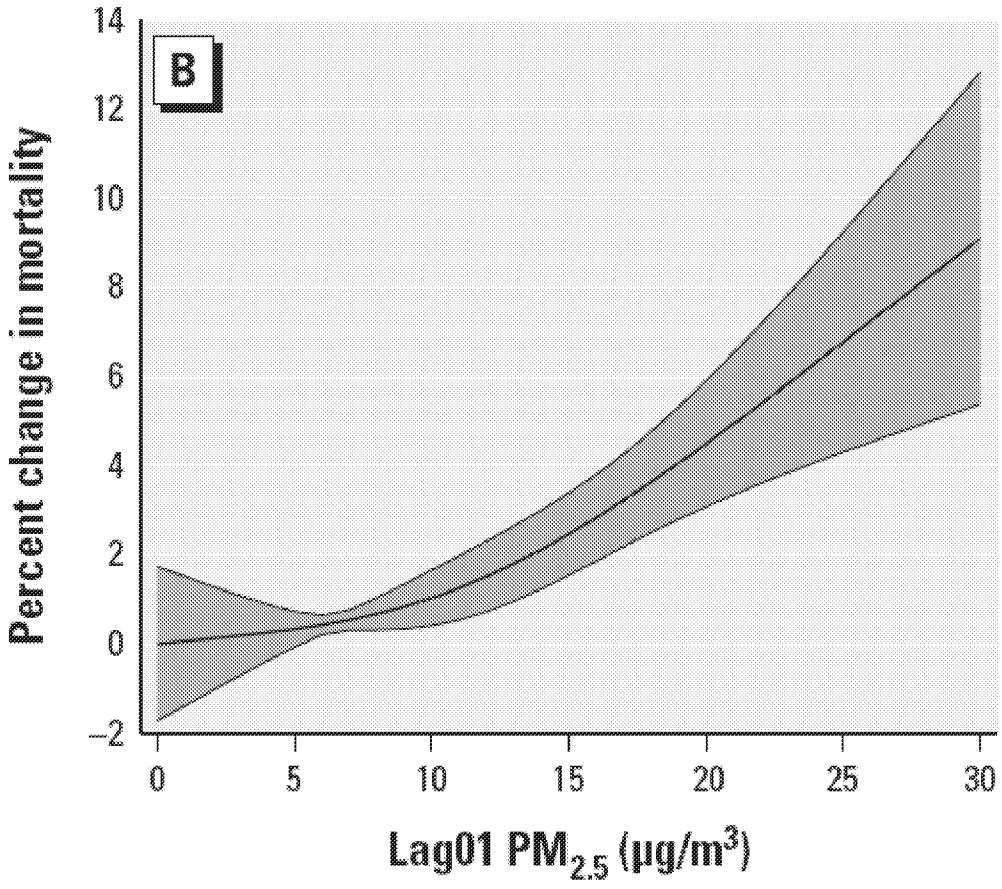
While most studies that examine the relationship between short-term $PM_{2.5}$ exposure and mortality focus on $PM_{2.5}$ mass, some studies have examined alternative exposure metrics, such as particle number concentration (NC), surface area concentration (SC), and mass concentration (MC) for PM size fractions smaller than $PM_{2.5}$ but larger than 100 nm. Particles smaller than 100 nm will be discussed in Section 11.5. To date, only a few studies examined PM size fractions smaller than 2.5 μm, and often these size fractions are included in studies that examine UFP exposure and mortality (Section 11.4.1). Across studies, generally positive associations were observed for particles >100 nm for NC, and <1.0 μm for SC and MC (See (U.S. EPA, 2018a)), which supports the larger body of evidence demonstrating a consistent, positive association between short-term $PM_{2.5}$ exposure and mortality. However, these studies are conducted over a short duration and are limited to two locations (i.e., China (Meng et al., 2013; Leitte et al., 2012; Breitner et al., 2011) and Spain (Pererz et al., 2009)). Additionally, although these studies report

generally positive associations it remains difficult to directly compare results from studies that use a NC or SC metric with the traditional mass based exposure metric.

11.1.10 Concentration-Response (C-R) Relationship and Threshold Analyses

Previous reviews of PM including the 2004 PM AQCD (U.S. EPA, 2004) along with the 2009 PM ISA (U.S. EPA, 2009) have highlighted the difficulty associated with examining the shape of the PM-mortality concentration-response (C-R) relationship and whether a threshold exists. Specifically, the 2004 AQCD and 2009 PM ISA stated that conducting C-R and threshold analyses is challenging due to the "(1) limited range of available concentration levels (i.e., sparse data at the low and high end); (2) heterogeneity of [at-risk] populations [between cities]; and (3) influence of measurement error" (U.S. EPA, 2004). Even with these inherent limitations, studies have continued to examine the PM-mortality C-R relationship and whether a threshold exists. In the 2009 PM ISA, the examination of the PM-mortality C-R relationship was limited to studies of PM_{10}. Within the multicity studies examined, there was evidence of a linear no-threshold C-R relationship between short-term PM exposures and mortality with some evidence of differences in the shape of the C-R curve across cities. A major limitation of the C-R analyses conducted to date has been the reliance on PM_{10} data and the limited amount of data available to examine the shape of the C-R curve at the low end of the concentration distribution. Recent studies conducted in the U.S. (Di et al., 2017a; Lee et al., 2015c; Shi et al., 2015) and Europe (Samoli et al., 2013) provide information specifically on the C-R relationship between short-term $PM_{2.5}$ exposures and mortality in different regions of the world and at $PM_{2.5}$ concentrations at the lower end of the distribution.

In a study of states in the New England region of the U.S., Shi et al. (2015) conducted two analyses to address (1) whether associations are observed at concentrations <30 $\mu g/m^3$ and (2) the shape of the PM-mortality C-R relationship at concentrations <30 $\mu g/m^3$. In the analysis restricted to person-time with $PM_{2.5}$ concentrations <30 $\mu g/m^3$ Shi et al. (2015) reported associations similar in magnitude (2.14% [95% CI: 1.33, 2.95]) to those observed in the full cohort that included $PM_{2.5}$ concentrations >30 $\mu g/m^3$ (2.14% [95% CI: 1.38, 2.89]). Using the restricted data set, Shi et al. (2015) then examined the shape of the C-R relationship between short-term $PM_{2.5}$ concentrations and mortality by fitting a penalized regression spline where the degrees of freedom (df) of the spline were selected by generalized cross-validation. The authors reported no evidence of deviation from linearity, but had less confidence in the shape of the curve at concentrations <5 $\mu g/m^3$ due to wider confidence intervals (Figure 11-11).

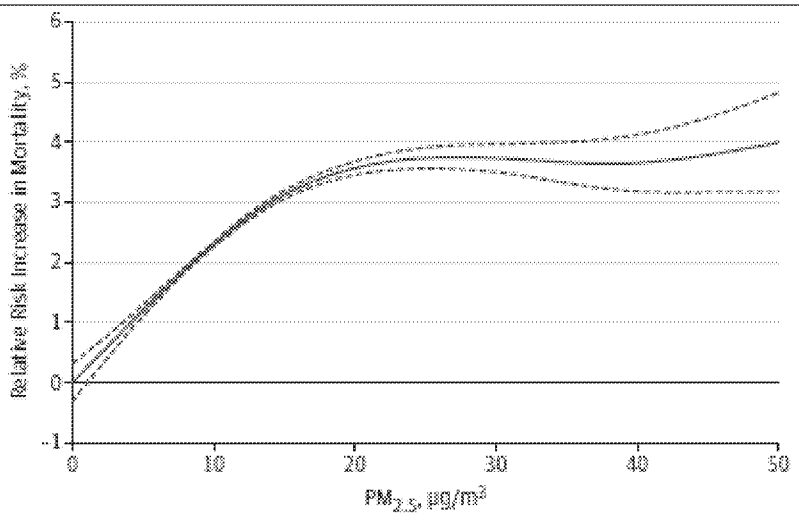


Source: Permission pending, Shi et al. (2015).

Figure 11-11 Concentration-response relationship between short-term $PM_{2.5}$ concentrations and mortality (lag 0–1) in an analysis restricted to person time with daily $PM_{2.5}$ concentrations <30 µg/m³.

Di et al. (2017a) examined the C-R relationship focusing on questions similar to those examined by Shi et al. (2015), but in a national analysis of the Medicare population. In a copollutant model with O_3 the authors examined: (1) whether associations are observed at $PM_{2.5}$ concentrations <25 µg/m³, and (2) the shape of the PM-mortality C-R relationship, particularly at concentrations <25 µg/m³. In the low exposure analysis, Di et al. (2017a) reported an association larger in magnitude (1.61 [95% CI: 1.48, 1.74]; lag 0–1) than the main analysis (1.05% [95% CI: 0.95, 1.15]; lag 0–1), indicating a steeper slope at lower $PM_{2.5}$ concentrations. The results of the low exposure analysis were confirmed when examining the shape of the C-R curve using penalized splines for both $PM_{2.5}$ and O_3, which reported evidence of an almost linear relationship with no evidence of a threshold and a steeper slope at concentrations <25 µg/m³ (Figure 11-12). While the low exposure results of Di et al. (2017a) differ from those of Shi et al. (2015),

this could be a reflection of the populations of the studies encompassing different age ranges (i.e., individuals over the age of 65, and the entire population, respectively).



Source: Permission pending, Di et al. (2017a).

Figure 11-12 Two-pollutant analysis of the $PM_{2.5}$ concentration-response (C-R) curve with penalized splines for both $PM_{2.5}$ and O_3 to examine the percent increase in daily mortality at lag 0–1 days.

Lee et al. (2015c) confirmed the findings of Shi et al. (2015) and Di et al. (2017a) that $PM_{2.5}$-mortality associations persist at low ambient $PM_{2.5}$ concentrations by conducting a subset analysis focusing on three southeastern U.S. states. The authors examined the association between short-term $PM_{2.5}$ exposure and mortality by limiting the dataset to zip codes where the predicted annual $PM_{2.5}$ concentrations were less than 12 $\mu g/m^3$ and in a separate analysis focused on ZIP codes where predicted 24-hour average $PM_{2.5}$ concentrations were less than 35 $\mu g/m^3$. In the full cohort the authors reported a 1.56% increase in mortality (95% CI: 1.19, 1.94) at lag 0−1. In the cut-point analyses focusing on the annual and daily cutpoints, Lee et al. (2015c) reported a 2.06% (95% CI: 1.97, 2.15) and 2.08% (95% CI: 1.99, 2.17) increase in mortality, respectively, providing evidence that $PM_{2.5}$-mortality associations remain and may be larger in magnitude at low $PM_{2.5}$ concentrations.

While Shi et al. (2015), Lee et al. (2015c), and Di et al. (2017a) examined the shape of the C-R relationship between short-term $PM_{2.5}$ exposure and mortality across a distribution of data, Samoli et al. (2013) focused exclusively on whether there is evidence of a threshold at specific concentrations. As part of the MED-PARTICLES project, the authors examined threshold values ranging from 0 to 35 $\mu g/m^3$ at increments of 5 $\mu g/m^3$ across the 10 Mediterranean cities included in the study. The threshold model

assumed the risk of mortality due to short-term $PM_{2.5}$ exposure was zero below the threshold value. Evidence of a threshold was examined in each city by computing the deviance of the fitted model for each threshold value, the authors then computed an average deviance across all cities. The deviance for each threshold value was then examined to determine whether any threshold values minimized the mean deviance. Samoli et al. (2013) did not observe any evidence of a threshold, with the models assuming no threshold reporting the lowest mean deviance, and subsequently being considered the "best-fitting" models. Although the 24-hour average $PM_{2.5}$ concentrations observed in the MED-PARTICLES cities were much higher than the $PM_{2.5}$ concentrations observed in Shi et al. (2015), the threshold analysis in Samoli et al. (2013) focusing on daily concentrations below 35 $\mu g/m^3$ provides additional support for a linear C-R relationship at concentrations relevant to U.S. cities.

Although difficulties remain in assessing the shape of the $PM_{2.5}$-mortality concentration-response relationship, as identified in the 2009 PM ISA, and studies have not conducted systematic evaluations of alternatives to linearity, recent studies continue to provide evidence of a no-threshold linear relationship, with less confidence at concentrations lower than 5 $\mu g/m^3$. Additionally, those studies that conducted analyses focused on examining associations at lower $PM_{2.5}$ concentrations provide initial evidence indicating that associations persist and may be larger in magnitude (i.e., a steeper slope) at lower $PM_{2.5}$ concentrations.

11.1.11 Associations between $PM_{2.5}$ Sources and Components and Mortality

The 2009 PM ISA examined the relationship between both $PM_{2.5}$ components and sources and individual health outcomes (e.g., mortality) and effects (e.g., blood pressure), as well as collectively across health outcomes, to assess whether any one source or component was more strongly related to a health outcome or effect. At the completion of the 2009 PM ISA, it was not evident that any one component or source was more strongly related to mortality, which was consistent with the broader conclusion on sources and components (U.S. EPA, 2009). Recent studies that examine both the relationship between short-term exposures to $PM_{2.5}$ components along with $PM_{2.5}$ mass provide additional evidence on whether $PM_{2.5}$ mass or an individual $PM_{2.5}$ component or source is more strongly associated with mortality.

11.1.11.1 $PM_{2.5}$ Components

The examination of the relationship between $PM_{2.5}$ components and mortality can generally be divided into two types of analyses: (1) those that examine whether specific components modify the $PM_{2.5}$-mortality association or (2) those that examine whether an individual component is associated with mortality and potentially a better indicator of PM toxicity compared to $PM_{2.5}$ mass. Although

approach (1) is considered one of the techniques used to assess component toxicity as detailed in Mostofsky et al. (2012) these studies are often used to examine heterogeneity in $PM_{2.5}$-mortality risk estimates. As a result, the focus of this section is on those techniques that fall under approach (2), which includes assessing $PM_{2.5}$ component effect by component concentration, component proportion, component concentration adjusted for $PM_{2.5}$ mass, component residual, or $PM_{2.5}$ residual (Mostofsky et al., 2012). Multicity $PM_{2.5}$ mortality studies detailed in the 2009 PM ISA examined associations with individual components (Ostro et al., 2008; Ostro et al., 2007), and indicated that a number of components are associated with mortality. However, there were limitations in the air quality data (i.e., 1-in-3 or 1-in-6 sampling of $PM_{2.5}$ components) and only a small number of studies had been conducted that examined the relationship between $PM_{2.5}$ components and mortality (U.S. EPA, 2009).

Since the completion of the 2009 PM ISA (U.S. EPA, 2009), a growing number of studies have examined the relationship between short-term exposure to $PM_{2.5}$ components and mortality. These studies continue to support the conclusions of the 2009 PM ISA that many components are associated with mortality and there is no evidence that any one component is more strongly associated with mortality than $PM_{2.5}$ mass. The recent multicity studies and U.S.-based single-city studies are detailed in Table 11-3 along with study specific details including statistical approach used to assess the $PM_{2.5}$ component effect and the $PM_{2.5}$ components examined.

Table 11-3 Study-specific details of multicity and U.S.-based single-city studies that examine the relationship between short-term exposure to $PM_{2.5}$ components and mortality.

Study	Mortality Outcome	Data/Sampling Schedule	Statistical Approach Used	Components Examined
Multicity studies				
Ostro et al. (2007) Six California counties, U.S. (2000–2003)	Cardiovascular	SLAMS; 1-in-3 or 1-in-6 day schedule	Individual components included in single pollutant model	Al, Br, Ca, Cl, Cu, EC, Fe, K, Mn, Ni, NO_3, OC, Pb, S, Si, SO_4, Ti, V, Zn
Ostro et al. (2008) Six California counties, U.S. (2000–2003)	Cardiovascular	SLAMS; 1-in-3 or 1-in-6 day schedule	Individual components included in single pollutant model	Ca, Cl, Cu, EC, Fe, K, NO_3, OC, S, Si, SO_4, Ti, Zn
†Krall et al. (2013) 72 U.S. cities (2000–2005)	Total	CSN; 1-in-3 or 1-in-6 day schedule	Individual components included in single pollutant model	EC, Na^+, NO_3, NH_4, OC, Si, SO_4

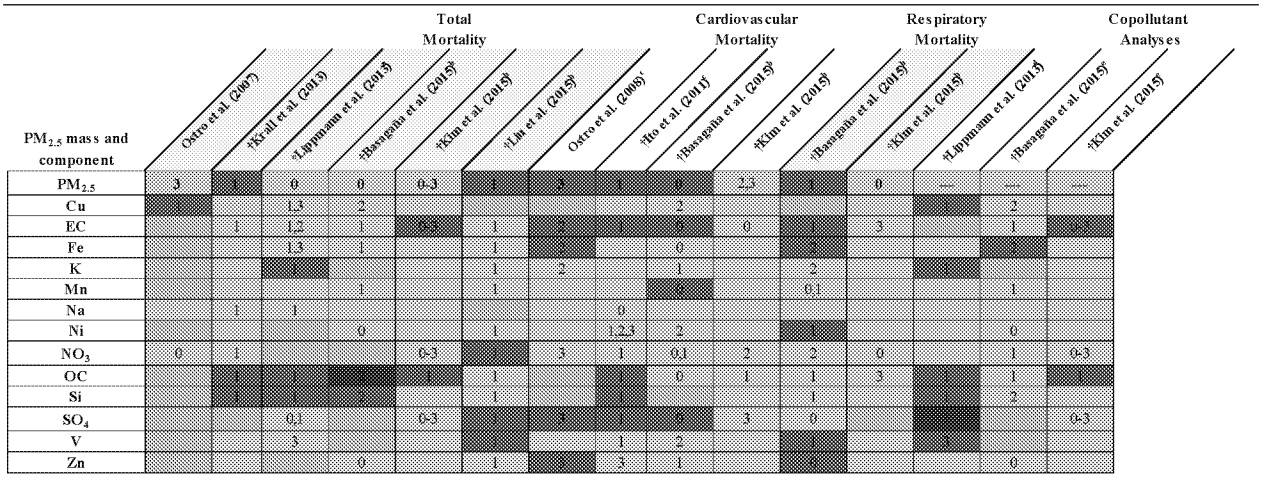
Table 11-3 (Continued): Study-specific details of multicity and U.S.-based single-city studies that examine the relationship between short-term exposure to $PM_{2.5}$ components and mortality.

Study	Mortality Outcome	Data/Sampling Schedule	Statistical Approach Used	Components Examined
†Lippmann et al. (2013a) 64 U.S. cities (2001–2006)	Total	CSN; 1-in-3 or 1-in-6 day schedule	(1) Individual components included in single pollutant model; (2) individual components in copollutant model with $PM_{2.5}$	As, Cu, EC, Fe, K, Na, Ni, NO_3^-, OC, Pb, SO_4^{2-}, Se, Si, V, Zn
†Basagaña et al. (2015) Five South-European cities (2003–2013)	Total Cardiovascular Respiratory	One monitor in each city; daily monitoring in two cities, biweekly monitoring in two cities, and once a week monitoring in one city	(1) Individual components included in single pollutant model; (2) individual component residual	Ca, Cu, EC, Fe, K, Mg, Mn, Ni, NO_3^-, OC, SO_4^{2-}, SiO_2, TC, Ti, V, Zn
Single-city studies				
†Kim et al. (2015) Denver, CO (2003–2007)	Total Cardiovascular Respiratory	Daily measurements from one monitor (DASH site)	(1) Individual components included in single pollutant model; (2) individual component residual	EC, NO_3^-, OC, SO_4^{2-}
†Liu and Zhang (2015) Houston, TX (2000–2011)	Total	CSN; 1-in-3 or 1-in-6 day schedule	Individual components included in single pollutant model	Al, Br, Cr, Cu, EC, Fe, K, Mn, Na^+, NH_4^+, Ni, NO_3^-, OC, Si, SO_4^{2-}, V, Zn
†Zhou et al. (2011) Detroit, MI Seattle, WA (2002–2004)	Total Cardiovascular Respiratory	Daily measurements from one monitor in each city	Individual components included in single pollutant model	Al, EC, Fe, K, Na, Ni, S, Si, V, Zn
†Ito et al. (2011) New York, NY (2000–2006)	Cardiovascular	Three CSN monitors; 1-in-3 day sampling	Individual components included in single pollutant model	Br, EC, Na^+, Ni, NO_3, OC, SO_4, Se, Si, V, Zn

AQS-TTN = U.S. EPA Air Quality System Technology Transfer Network; CSN = Chemical Speciation Network; DASH = Denver Aerosol Sources and Health study; STN = Speciation Trends Network; SLAMS = State and Local Air Monitoring Stations Network.
†Studies published since the 2009 PM ISA.

As detailed in Table 11-3 and throughout the text that follows, the evaluation of the association between $PM_{2.5}$ components and mortality is complicated by the different methods applied across studies. Overall, the results for individual $PM_{2.5}$ components across studies are generally more imprecise than the results for $PM_{2.5}$ (i.e., much wider confidence intervals, often including the null value), which make the individual results, as well as results across studies, more difficult to interpret. As such, for the purposes of characterizing results with respect to $PM_{2.5}$ components a different convention is employed to evaluate the pattern of associations across studies. Specifically, risk estimates from studies are classified into four categories in Figure 11-13 and Figure 11-14: (1) statistically significant positive associations; (2) positive

associations, regardless of width of the confidence interval; (3) null or negative association; and (4) statistically significant negative association. Figure 11-13 and Figure 11-14 summarize the results from studies that examined associations between short-term $PM_{2.5}$ mass and $PM_{2.5}$ components that will be evaluated in the following section.



[a]Lippmann et al. (2013a) results representative of median interquartile range increase in individual $PM_{2.5}$ component concentrations for the 64 cities combined.

[b]Results representative of an interquartile range increase in individual $PM_{2.5}$ component concentrations.

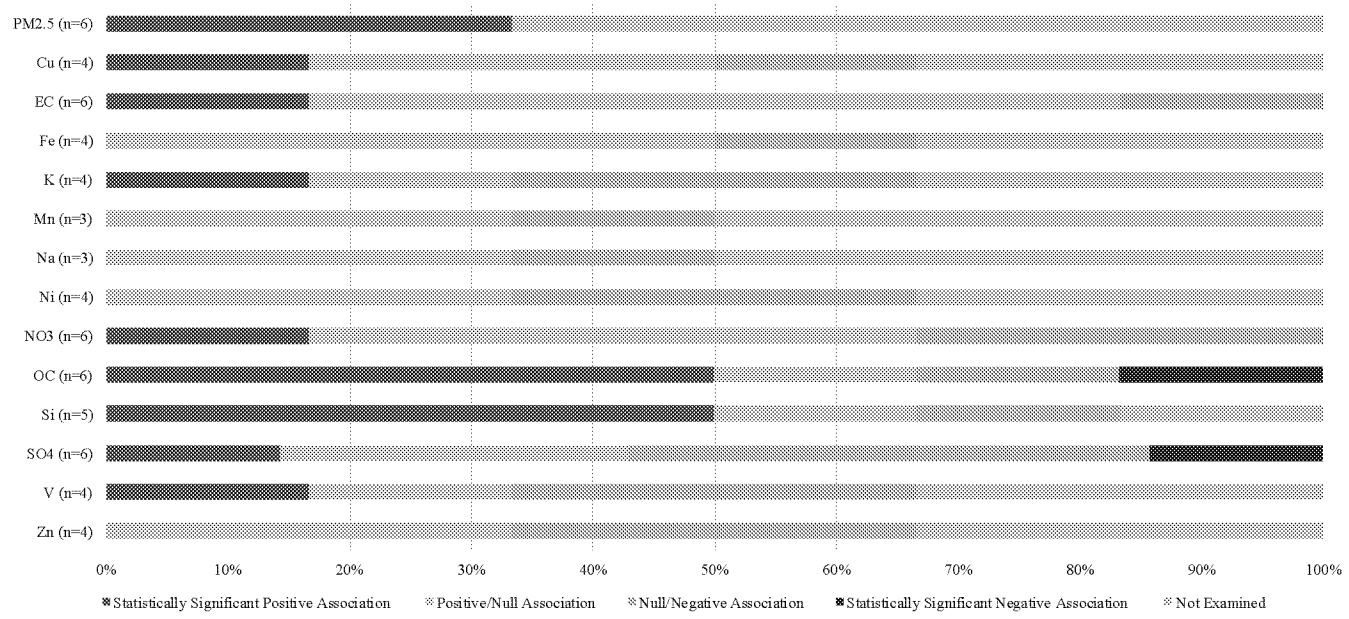
[c]Studies only examined $PM_{2.5}$ component associations with cardiovascular mortality.

[d]Lippmann et al. (2013a) results representative of median interquartile range increase in individual $PM_{2.5}$ component concentrations for the 64 cities combined in copollutant model with $PM_{2.5}$.

[e]Basagaña et al. (2015) results using the $PM_{2.5}$ component residual method detailed by Mostofsky et al. (2012).

Note: †$PM_{2.5}$ component studies published since the 2009 PM ISA. $PM_{2.5}$ row = lag(s) at which association observed between short-term $PM_{2.5}$ exposure and mortality; $PM_{2.5}$ components rows = lag(s) at which association observed. Dark blue = study reported statistically significant positive association; Light blue = study reported a positive association regardless of width of confidence intervals; Light orange = study reported null or negative association; Red = study reported statistically significant negative association; Gray = study did not examine individual component. Only those $PM_{2.5}$ components that were examined in at least three studies that included results for total (nonaccidental) mortality are included in this table.

Figure 11-13 Heat map of associations observed between short-term $PM_{2.5}$ and $PM_{2.5}$ components exposure and mortality in multi- and single-city studies.



N = number of studies that provided an estimate for $PM_{2.5}$ mass and individual $PM_{2.5}$ components.

Note: Bars represent the percent of associations across studies for $PM_{2.5}$ mass or $PM_{2.5}$ components detailed in Figure 11-13 that are statistically significant positive (dark blue), positive/null (light blue), null/negative (light orange), statistically significant negative (red), or not examined (gray).

Figure 11-14 Distribution of total (nonaccidental) mortality associations for $PM_{2.5}$ and $PM_{2.5}$ components examined in studies detailed in Figure 11-13.

Single Component Models

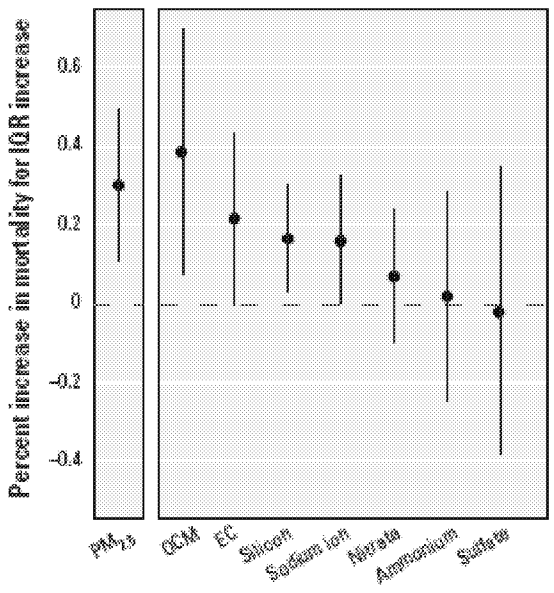
At the completion of the 2009 PM ISA, most studies that examined the association between short-term exposure to $PM_{2.5}$ components and mortality consisted of statistical models that examined component-mortality associations one at a time. Although informative, these studies are often difficult to interpret because they do not account for the individual component being part of $PM_{2.5}$ mass. Additionally, although often not reported, the correlations between individual $PM_{2.5}$ components and $PM_{2.5}$ mass are often moderate ($r = 0.4–0.7$) to high ($r > 0.7$), which complicates the interpretation of the single-component model results. Recent multi- and single-city studies have continued to examine $PM_{2.5}$ component-mortality associations in single component models, but the addition of seasonal analyses for some studies have attempted to gain a broader understanding of how $PM_{2.5}$ mass and overall composition may change over the course of the year and affect health.

Multicity studies conducted by Lippmann et al. (2013a) as part of the NPACT study and Krall et al. (2013) in 72 U.S. cities, both primarily focused on single-component models to assess the relationship between $PM_{2.5}$ components and mortality. Lippmann et al. (2013a) examined the association between short-term exposure to $PM_{2.5}$ components, along with sources (see Section 11.1.11.2), across 64 U.S. cities. The components selected to be examined were based on analyses of measurements obtained, in

reference to both the detection limit and fraction of readings equaling zero; monitor-to-monitor correlations for a subset of cities; and toxicological considerations (Lippmann et al., 2013a). In the main analyses, the authors did not use measured component data, but instead calculated the daily deviation from the monthly mean in an attempt to "reduce the influence of the seasonal cycles of pollutants on the overall associations" (Lippmann et al., 2013a). In single-component models in an all-year analysis, the strongest associations were for Cu, K, OC, Si, and V although at different lags ranging from 1 to 3 days, while the $PM_{2.5}$ association was positive at lag 0 (Figure 11-13). In seasonal analyses, the $PM_{2.5}$ association was strongest in the warm season at lag 0 with no evidence of an association in the cold season. Across components strong positive associations were only observed at lag 0 for Na, NO_3^-, and SO_4^{2-}, while other components were found to be positively associated at other lags including: EC, K, Na, OC, Pb, Si, and V. A different pattern of associations was observed in the cold season with evidence of positive associations across lags for As, Cu, EC, K, OC, Se, and Si. The different lag structure of associations for the individual components compared to $PM_{2.5}$ mass complicates the interpretation of the individual component results.

Krall et al. (2013) took a slightly different approach than Lippmann et al. (2013a) in an analysis of 72 U.S. cities, by focusing on those components that contribute the most (i.e., approximately 79−85%) of yearly and seasonal $PM_{2.5}$ mass. The authors developed city-specific component models and also examined associations by season (i.e., spring, summer, fall, and winter) and by region (i.e., Northeast, Southeast, southern Midwest, northern Midwest, Southwest, and Northwest). Krall et al. (2013) observed the strongest associations for OCM, EC, Si, and Na^+, but overall reported no evidence that any of these components is more strongly associated with mortality than $PM_{2.5}$ mass (Figure 11-15). Additionally, the authors reported no evidence that individual component associations varied by season or region.

In addition to the U.S. based multicity studies detailed above, Basagaña et al. (2015) examined the association between short-term exposure to $PM_{2.5}$ components and mortality in five cities in southern Europe as part of the MED-PARTICLES project. The components examined were selected a priori and based on their detectability in each of the five cities as well as evidence from the literature linking each of the $PM_{2.5}$ components with health. In single-component models the authors observed the strongest associations with SiO_2 and total (nonaccidental) mortality; SiO_2, Mg, and Mn and cardiovascular mortality; and SO_4^{2-}, K, and Mn and respiratory mortality.



Source: Permission pending, Krall et al. (2013).

Figure 11-15 Percent increase in mortality for $PM_{2.5}$ and $PM_{2.5}$ components for an interquartile range (IQR) increase in concentrations at lag 1 across 72 U.S. cities.

U.S.-based single-city studies conducted in locations across the country provide additional information that can aid in the interpretation of $PM_{2.5}$ component results from multicity studies. In a study conducted in New York City, NY focusing on cardiovascular mortality, Ito et al. (2011) examined associations with $PM_{2.5}$ components that were selected for inclusion in the study "based on past source apportionment studies in New York City as well as recent health effects studies". In all-year analyses, when focusing on those components that are the largest contributors to $PM_{2.5}$ mass, the authors observed the strongest associations for EC, OC, and SO_4^{2-} at lag 1. These results persisted in the warm season, but in the cold season the association remained the strongest for EC, and although the positive magnitude of the association and precision were reduced for OC and SO_4^{2-}. Among the other components examined, associations were observed in all-year and seasonal analyses for Br and Na^+, whereas for Se there was evidence of an association in all-year and warm season analyses at lag 1, but not in the cold season. For Ni, V, and Zn, there was no evidence of an association in all-year or warm season analyses, but lag 3 in the cold season, which is consistent with the burning of residual oil in NYC (see Section 11.1.11.2).

Although Ito et al. (2011) examined seasonal differences in $PM_{2.5}$ component associations, the authors were limited by the one-in-three sampling schedule of the monitors. Examining the associations between total, cardiovascular and respiratory mortality and $PM_{2.5}$ components, Zhou et al. (2011) was able to more rigorously examine potential differences in seasonal associations (i.e., examine both single and multiday lags) compared to Ito et al. (2011) due to the availability of daily $PM_{2.5}$ component data.

Similar to other component studies detailed in this section, the authors selected $PM_{2.5}$ components for inclusion in the study based on evidence from the toxicological literature. When examining the seasonal pattern of associations using a distributed lag model for 0−2 days, there was a clear difference in potential sources of $PM_{2.5}$ based on the strongest $PM_{2.5}$ associations with total and cause-specific mortality occurring in the warm season for Detroit and the cold season for Seattle (see Section 11.1.11.2). In both locations, mean 24-hour average $PM_{2.5}$ concentrations were near of below15 $\mu g/m^3$ for the duration of the study (Detroit = 15.1 $\mu g/m^3$; Seattle = 9.7 $\mu g/m^3$). The seasonal pattern in $PM_{2.5}$ mass associations observed in both cities were further reflected when examining $PM_{2.5}$ component associations. In Detroit in the warm season for total (nonaccidental) mortality there was evidence of positive associations for S and EC, with a strong negative association for Si. This pattern of associations was similar for cardiovascular mortality, although the confidence intervals for each component were larger. Wider confidence intervals were also observed for respiratory mortality, with positive associations only for Ni and S. For Seattle in the cold season, the component associations observed for total (nonaccidental) mortality and cardiovascular mortality were similar with positive associations observed for Al, Fe, K, Ni, S, Si, Zn, and EC. Additionally, there was some evidence of a positive association between only cardiovascular mortality and V. When examining respiratory mortality in Seattle there was no evidence of a positive association with any $PM_{2.5}$ components. In both the Detroit and Seattle data sets, Zhou et al. (2011) conducted sensitivity analyses focusing on model specification and did not observe any evidence that $PM_{2.5}$ component-mortality associations changed when increasing the degrees of freedom to control for temporal trends or when using alternative temperature variables, which is similar to what has been observed when examining $PM_{2.5}$ mass (see Section 11.1.5.1).

Kim et al. (2015) also used daily $PM_{2.5}$ component data in a study in Denver, CO that examined total (nonaccidental), cardiovascular, and respiratory mortality. However, unlike a number of the studies focusing on $PM_{2.5}$ components the authors only focused on a few of the main contributors to $PM_{2.5}$ mass (i.e., EC, OC, SO_4^{2-}, and NO_3^-). Across mortality outcomes, the strongest associations were observed for total (nonaccidental) mortality for the 0−3 distributed lag model results for EC and OC, with less evidence of an association for SO_4^{2-} and NO_3^-. For cardiovascular mortality there was only evidence for a positive association with OC and lag 1; whereas for respiratory mortality there was evidence of a positive association at lag 3 for both EC and OC. Similar to Zhou et al. (2011) in sensitivity analyses focusing on model specification the authors did not observe that $PM_{2.5}$ component-mortality associations changed when increasing the degrees of freedom to control for temporal trends or when using alternative temperature variables.

As detailed above, the majority of $PM_{2.5}$ component studies have examined whether one or a combination of components are driving the $PM_{2.5}$ mass associations, but Liu and Zhang (2015) examined whether associations with $PM_{2.5}$ mass and components have changed over time. The design of this study is like that of Dominici et al. (2007) which also attempted to examine whether PM-mortality risks have changed over time, but on a national scale. As detailed in the 2009 PM ISA, "a flaw in the use of the time-series study design for this type of analysis is that it adjusts for long-term trends, and therefore, does

not estimate the change in mortality in response to the gradual change in [PM]." As a result, the focus is on the $PM_{2.5}$ mass and component results detailed for the entire study period along with the seasonal analyses. Similar to previous studies, the components examined were selected a priori and based on evidence from the epidemiologic literature as well as a local source apportionment study (Liu and Zhang, 2015). When focusing on associations at lag 1, $PM_{2.5}$ mass had the strongest association, with evidence of a positive association for a number of individual components (Figure 11-13). When conducting seasonal analyses, the strongest associations tended to be observed during the winter, specifically for NH_4^+, Br, Cr, Mn, Ni, SO_4^{2-}, NO_3^-, V, EC, and OC. The seasonal component results are consistent with the $PM_{2.5}$ results where the association with the largest magnitude was also observed to be in the winter.

Additional $PM_{2.5}$ Component Analyses

The majority of $PM_{2.5}$ component studies conducted to date have focused almost exclusively on examining single-component models. However, a main limitation of single component models is their inability to account for the potential confounding effects of $PM_{2.5}$ mass or other $PM_{2.5}$ components. As detailed in Mostofsky et al. (2012) there are a number of alternative statistical approaches that can be used, each with their own strengths and limitations. A few of the studies detailed above that focused on single pollutant models also examined alternative models to further inform the $PM_{2.5}$ component-mortality relationship.

Lippmann et al. (2013a) used a traditional two-pollutant (i.e., copollutant) model in an attempt to examine whether $PM_{2.5}$ mass confounds the component associations observed for a subset of the components examined. In an all-year analysis, component results were robust to inclusion of $PM_{2.5}$ in the model for OC, V, Si, K, and Cu, with evidence of potential confounding for EC and SO_4^{2-}, but these two components contribute a large percentage to $PM_{2.5}$ mass and are often found to be highly correlated. In seasonal analyses, all components were robust to the inclusion of $PM_{2.5}$ in the model in the warm season, with some evidence of attenuation of the component association in the cold season for V, Si, K, and Cu, while SO_4^{2-} was found to be negatively associated with mortality.

Instead of applying a traditional copollutant model to examine component associations, Basagaña et al. (2015) and Kim et al. (2015) used the component residual approach. In this approach, the residuals from the regression of $PM_{2.5}$ on each component are included in the model, which provides the effect of each individual component holding $PM_{2.5}$ constant and theoretically eliminates confounding by $PM_{2.5}$ (Mostofsky et al., 2012). As detailed in Table 11-3, Basagaña et al. (2015) reported evidence that component results were relatively robust using the component residual approach to examine associations. Similarly, Kim et al. (2015) reported that individual component associations were relatively consistent with those observed in single-component models when using the component residual approach (Figure 11-13).

Summary

Since the completion of the 2009 PM ISA there has been a growing body of single and multicity epidemiologic studies that examined the association between short-term exposures to $PM_{2.5}$ components and mortality. As depicted in Figure 11-13, $PM_{2.5}$ component studies reported positive associations with multiple PM components at various lags using both single component models as well as alternative models. Studies have demonstrated positive associations with a number of $PM_{2.5}$ components, but across studies there is a varying degree to which components have been found to be positively associated with mortality. In comparison, there is evidence of consistent positive associations between $PM_{2.5}$ mass and mortality across all studies examined (Figure 11-14). As demonstrated in some studies the different pattern of component associations is reflective of the different sources of $PM_{2.5}$ across cities. Collectively, recent studies further support the conclusions of the 2009 PM ISA, indicating that many $PM_{2.5}$ components are associated with mortality, but no one component is more strongly associated with mortality than $PM_{2.5}$ mass.

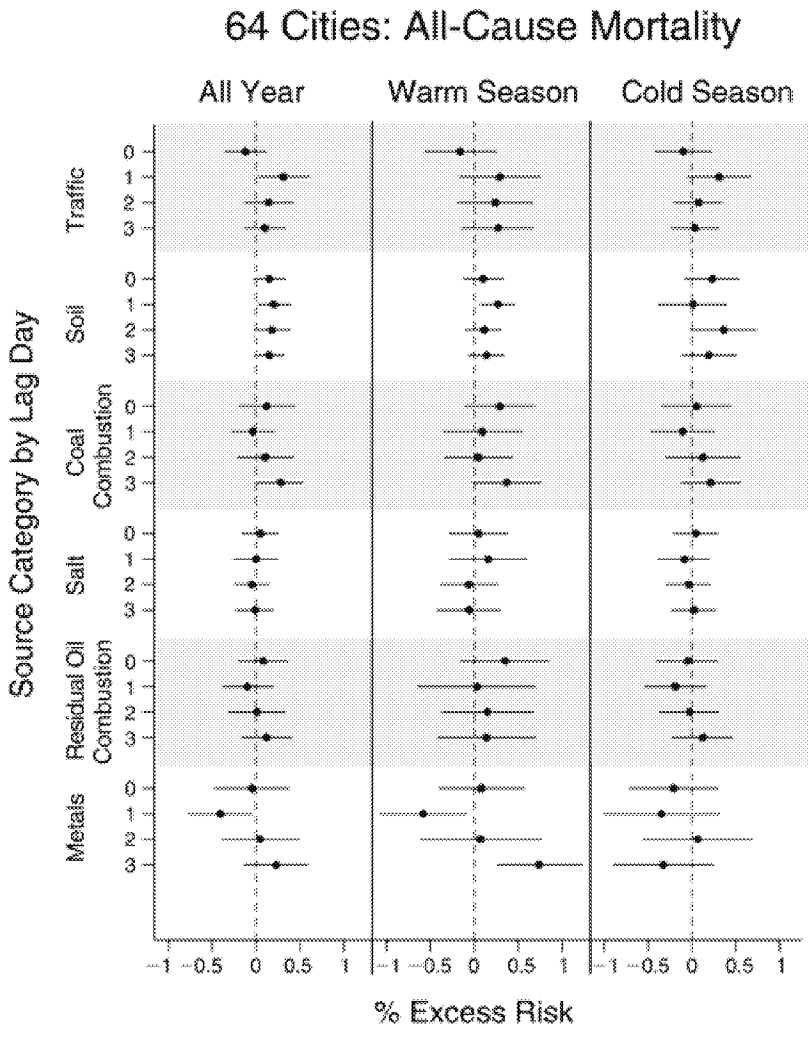
11.1.11.2 Sources

A few studies evaluated in the 2009 PM ISA conducted source apportionment analyses to examine whether specific sources of $PM_{2.5}$ are more strongly associated with mortality. These studies generally found that the most consistent associations were for $PM_{2.5}$ from combustion-related activities, which supports the results from studies evaluated in the 2004 PM AQCD (U.S. EPA, 2004). Recent studies focus primarily on examining individual $PM_{2.5}$ component associations, but also often link the components evaluated to specific $PM_{2.5}$ sources a priori. As a result, most recent studies do not rely on formal mathematical approaches, such as source apportionment, to identify sources in the context of examining the relationship between source exposures and daily mortality. As detailed in the Preface , the evaluation of associations between health effects and sources is limited to those studies that use mathematical approaches and do not identify sources a priori.

Within the NPACT study Lippmann et al. (2013a) conducted a factor analysis to identify $PM_{2.5}$ sources. The factor analysis was conducted at the national level using both $PM_{2.5}$ components along with gaseous pollutant data from all 64 U.S. cities to identify source categories: traffic (EC, OC, and NO_2), soil (Al, Si, and Ti), coal combustion (As, Se, and SO_2), residual oil combustion (Ni and V), salt (Na and Cl), and metals (Fe, Mn, and Zn). These source categories were then applied to each of the 64 U.S. cities to see which sources were found in each city. Because the source categories were based on a mathematical model they may not be representative of the sources in each city, and the interpretation of a source category on a city-to-city basis may be different (Lippmann et al., 2013a).

When examining source categories in each city, the number of cities that were found to encompass each of the source categories varied. Across cities, the sources identified in each varied with 63 cities having a traffic and soil source, 46 cities having a coal combustion source, 42 cities having a salt

source, 29 cities having a residual oil combustion source, and 16 cities having a metals source. The results of the source analysis using the individual city results and the national results were found to be relatively similar. As depicted in Figure 11-16, in all-year and seasonal analyses multiple sources were found to be associated with mortality at a number of lags.



Source: Permission pending, Lippmann et al. (2013a).

Figure 11-16 Percent increase in total (nonaccidental) mortality for individual cities within the 64 U.S. cities examined in the National Particle Component Toxicity (NPACT) study for a median interquartile range (IQR) increase in factor scores for the cities combined.

In addition to Lippmann et al. (2013a) where specific sources where defined using statistical approaches, Kollanus et al. (2016) examined whether there was evidence of differential effects on days impacted by vegetative fires (i.e., smoke days) compared to regular (i.e., nonsmoke) days in Helsinki, Finland. The authors predicted surface smoke concentrations at 1°×1° grid cells, and defined smoke days using three approaches: (1) 24-hour average $PM_{2.5}$ concentrations at urban background site ≥25 μg/m^3; (2) 24-hour average $PM_{2.5}$ or PM_{10} concentration at regional background site ≥20 μg/m^3; or (3) the smoke prediction model indicated abundant or some smoke due to long-range transport from vegetative fires. On smoke days, mean $PM_{2.5}$ concentrations were more than three times higher than nonsmoke says (i.e., 30 μg/m^3 vs. 8.6 μg/m^3); however, only 72 days during the 10-year study period were classified as smoke days. When comparing smoke to nonsmoke days, the percent increase in nonaccidental mortality was almost double on smoke days (i.e., lag 2: 2.5−2.7% for all ages and ≥65 years, respectively), but dramatically larger when examining cardiovascular mortality where there was no evidence of an association for nonsmoke days (i.e., 8.0−13.8% across individual lags of 0 and 3 day for all ages and ≥65 years).

In summary, when examining sources of $PM_{2.5}$, the results of the limited number of recent studies further support studies evaluated in the 2004 PM AQCD and 2009 PM ISA, demonstrating that combustion-related sources are often found to be associated with mortality. Collectively, the results of recent studies that examined the association between $PM_{2.5}$ sources and mortality are consistent with the conclusions of the 2009 PM ISA.

11.1.12 Summary and Causality Determination

Recent multicity studies evaluated since the completion of the 2009 PM ISA continue to provide evidence of primarily positive associations between short-term $PM_{2.5}$ exposures and total (nonaccidental) mortality from studies conducted mostly in urban areas using traditional exposure assignment approaches (i.e., average of all available monitors) as well as studies with a larger spatial coverage (i.e., urban and rural areas) employing new methods using all available $PM_{2.5}$ data (i.e., combination of monitoring, satellite and LUR). Additionally, the evidence from recent studies further substantiates the relationship between short-term $PM_{2.5}$ exposure and mortality by providing additional information on potential copollutant confounding; effect modification (e.g., stressors, pollutants, season); geographic heterogeneity in associations; and the shape of the C-R relationship, which collectively reaffirms that a causal relationship exists between short-term $PM_{2.5}$ exposure and mortality. The body of evidence for total mortality is supported by generally consistent positive associations with cardiovascular and respiratory mortality. Although there is coherence of effects across the scientific disciplines (i.e., animal toxicological, controlled human exposure studies, and epidemiologic) and biological plausibility for $PM_{2.5}$-related cardiovascular (Chapter 6) and respiratory (Chapter 5) morbidity, there is strong evidence indicating biological plausibility for $PM_{2.5}$-related cardiovascular mortality with more limited evidence for respiratory mortality. This section describes the evaluation of evidence for total (nonaccidental)

mortality, with respect to the causality determination for short-term exposures to $PM_{2.5}$ using the framework described in Table II of the Preamble to the ISAs (U.S. EPA, 2015b). The key evidence, as it relates to the causal framework, is summarized in Table 11-4.

Table 11-4 Summary of evidence for a causal relationship between short-term $PM_{2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Consistent epidemiologic evidence from multiple, high quality studies at relevant $PM_{2.5}$ concentrations	Increases in mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia. Total mortality associations, further supported by increases in cardiovascular and respiratory mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia.	Section 11.1.2 Figure 11-1 Figure 11-2 Section 5.1.9 Section 6.1.9	Mean 24-h avg: U.S. and Canada: 4.37–17.97 Europe: 13–27.7[d] Asia: 11.8–69.9 Table 11-1
Epidemiologic evidence from copollutant models provides some support for an independent $PM_{2.5}$ association	The magnitude of $PM_{2.5}$ associations remain positive, but in some cases are reduced with larger confidence intervals in copollutant models with gaseous pollutants and $PM_{10-2.5}$, supporting the limited evidence from the 2009 PM ISA. Further support from copollutant analyses indicating positive associations for cardiovascular and respiratory mortality. Recent studies that examined potential copollutant confounding are limited to studies conducted in Europe and Asia. When reported, correlations with gaseous copollutants were primarily in the low ($r < 0.4$) to moderate ($r \geq 0.4$ or <0.8) range.	Section 11.1.4 Figure 11-3 Section 5.1.10.1 Section 6.1.14.1	
Epidemiologic evidence supports a linear, no-threshold concentration-response (C-R) relationship	Recent multicity studies conducted in the U.S. and Europe provide direct evidence of a linear, no-threshold C-R relationship at lower $PM_{2.5}$ concentrations with initial evidence of a steeper slope, but extensive systematic evaluations of alternatives to linearity have not been conducted.	Section 11.1.10 Shi et al. (2015) Lee et al. (2015c) Di et al. (2017a)	

Table 11-4 (Continued): Summary of evidence indicating that a causal relationship exists between short-term $PM_{2.5}$ exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Biological plausibility from cardiovascular morbidity evidence	Strong evidence for coherence of effects across scientific disciplines and biological plausibility for a range of cardiovascular effects in response to short-term $PM_{2.5}$ exposure, specifically for ischemic events and heart failure, which is supported by experimental evidence and epidemiologic studies examining hospital admissions and ED visits. The collective body of cardiovascular morbidity evidence provides biological plausibility for a relationship between short-term $PM_{2.5}$ exposure and cardiovascular mortality, which comprises ~33% of total mortality.[e]	Section 6.1.16 Table 6-33	
Limited biological plausibility from respiratory morbidity evidence	Limited evidence for coherence of effects across scientific disciplines and biological plausibility, with the strongest evidence for exacerbations of COPD and asthma. The collective body of respiratory morbidity evidence provides limited biological plausibility for a relationship between short-term $PM_{2.5}$ exposure and respiratory mortality, which comprises ~9% of total mortality.[e]	Section 5.1.12 Table 5-18	
Uncertainty regarding geographic heterogeneity in $PM_{2.5}$ associations	Multicity U.S. studies demonstrate city-to-city and regional heterogeneity in $PM_{2.5}$-mortality associations. Evidence supports that a combination of factors including composition and exposure factors may contribute to the observed heterogeneity.	Section 11.1.6.3	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015b).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to the causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

[d]Median concentration from Samoli et al. (2013).

[e]Statistics taken from NHLBI (2017).

Collectively, the evidence from recent multicity studies of short-term $PM_{2.5}$ exposures and mortality primarily demonstrates positive associations with total (nonaccidental) mortality, with increases ranging from 0.19% (Lippmann et al., 2013a) to 2.80% (Kloog et al., 2013) at lags of 0 to 1 days in single-pollutant models. These results are further supported by initial studies employing causal inference and quasi-experimental statistical approaches (Section 11.1.2.1). Whereas most studies rely on assigning exposure using data from ambient monitors, some recent studies have also employed approaches that use

all available $PM_{2.5}$ data (i.e., monitor, satellite, and LUR) allowing for the inclusion of less urban and rural locations in analyses (Lee et al., 2015c; Shi et al., 2015; Kloog et al., 2013). Recent studies expand the assessment of potential copollutant confounding on the $PM_{2.5}$-mortality relationship, and provide additional evidence supporting that $PM_{2.5}$ associations remain positive and relatively unchanged in copollutant models with both gaseous pollutants and $PM_{10-2.5}$, but this assessment is limited to multicity studies conducted in Europe and Asia where mean 24-hour average $PM_{2.5}$ concentrations are higher (Table 11-4). However, the low ($r < 0.4$) to moderate correlations ($r = 0.4 < 0.7$ between $PM_{2.5}$ and gaseous pollutants and $PM_{10-2.5}$ increase the confidence in $PM_{2.5}$ having an independent effect on mortality.

The positive associations for total (nonaccidental) mortality reported across the majority of studies evaluated is further supported by analyses focusing on cause-specific mortality that continue to provide evidence of generally consistent positive associations with both cardiovascular and respiratory mortality, except in the case of a multicity study conducted in Europe (Lanzinger et al., 2016). Risk estimates for cardiovascular mortality ranged from 0.09% (Lippmann et al., 2013a) to 2.32% (Lee et al., 2015c) while those for respiratory mortality ranged from 0.09% (Lee et al., 2015c) to 2.30% (Janssen et al., 2013), but overall associations tend to be larger in magnitude for respiratory mortality. For both cardiovascular and respiratory mortality there was a limited assessment of potential copollutant confounding, but for both outcomes initial evidence indicates that associations remain positive and relatively unchanged in models with gaseous pollutants and $PM_{10-2.5}$, further supporting the copollutant analyses conducted for total (nonaccidental) mortality. The strong evidence for ischemic events and heart failure as detailed in the assessment of cardiovascular morbidity (Chapter 6), provide strong biological plausibility for $PM_{2.5}$-related cardiovascular mortality, which comprises the largest percent of total mortality (i.e., ~33%) (NHLBI, 2017). Although there is evidence for exacerbations of COPD and asthma, the collective body of respiratory morbidity evidence provides limited biological plausibility for $PM_{2.5}$-related respiratory mortality (Chapter 5).

In addition to examining potential copollutant confounding, a number of studies also assessed whether statistical models adequately account for temporal trends and weather covariates. Across studies that evaluated model specification, $PM_{2.5}$-mortality associations remained positive, although in some cases were attenuated, when using different approaches to account for temporal trends or weather covariates (Section 11.1.5). Seasonal analyses continue to provide evidence that associations are larger in magnitude during warmer months, but it remains unclear if copollutants confound the associations observed. In addition to seasonal analyses, some studies also examined whether temperature modifies the $PM_{2.5}$-mortality relationship. Initial evidence indicates that the $PM_{2.5}$-mortality association may be larger in magnitude at lower and higher temperatures, but this observation has not been substantiated by studies conducted in the U.S. (Section 11.1.6.2).

At the completion of the 2009 PM ISA, one of the main uncertainties identified was the regional and city-to-city heterogeneity in $PM_{2.5}$-mortality associations observed in multicity studies. Recent studies

examined both city specific as well as regional characteristics to identify the underlying factors that contribute to this heterogeneity (Section 11.1.6.3). Analyses focusing on effect modification of the $PM_{2.5}$-mortality relationship by $PM_{2.5}$ components, regional patterns in $PM_{2.5}$ components and city-specific differences in composition and sources indicate some differences in the $PM_{2.5}$ composition and sources across cities and regions, but these differences do not fully explain the heterogeneity observed. Additional studies examined whether exposure factors play a role in explaining the heterogeneity in $PM_{2.5}$-mortality associations and found that some factors related to housing stock and commuting as well as city-specific factors (e.g., land-use, port volume, and traffic information) also explain some of the observed heterogeneity. Collectively, recent studies indicate that the heterogeneity in $PM_{2.5}$-mortality risk estimates cannot be attributed to one factor, but instead a combination of factors including, but not limited to, compositional and source differences as well as exposure differences.

A number of recent studies conducted systematic evaluations of the lag structure of associations for the $PM_{2.5}$-mortality relationship by examining either a series of single-day or multiday lags and these studies continue to support an immediate effect (i.e., lag 0 to 1 days) of short-term $PM_{2.5}$ exposures on mortality (Section 11.1.8.1). Recent studies also conducted analyses comparing the traditional 24-hour average exposure metric with a subdaily metric (i.e., 1-hour max). These initial studies provide evidence of a similar pattern of associations for both the 24-hour average and 1-hour max metric, with the association larger in magnitude for the 24-hour average metric. Additionally, some studies examined alternative exposure metrics representing size fractions smaller than $PM_{2.5}$ and reflecting NC and SC. The generally positive associations reported with mortality for these smaller PM size fractions support the larger body of $PM_{2.5}$-mortality evidence, but it is difficult to compare NC and SC metrics with the traditional mass-based metric.

Building off the initial analysis of the C-R relationship between short-term PM exposure and mortality that focused on PM_{10}, recent multicity studies conducted in the U.S. and Europe examined the shape of the C-R relationship and whether a threshold exists specifically for $PM_{2.5}$ (Section 11.1.10). These studies have used different statistical approaches and consistently demonstrated a linear relationship with no evidence of a threshold. Additionally, recent analyses conducted at lower $PM_{2.5}$ concentrations (i.e., 24-hour average $PM_{2.5}$ concentrations <30 $\mu g/m^3$) provide initial evidence indicating that $PM_{2.5}$-mortality associations persist and may be stronger (i.e., a steeper slope) at lower concentrations. However, to date, studies have not conducted extensive analyses exploring alternatives to linearity when examining the shape of the $PM_{2.5}$-mortality C-R relationship.

Overall, recent epidemiologic studies build upon and further reaffirm the conclusions of the 2009 PM ISA for total mortality. The evidence particularly from the assessment of $PM_{2.5}$-related cardiovascular morbidity, with more limited evidence from respiratory morbidity, provides biological plausibility for mortality due to short-term $PM_{2.5}$ exposures. In conclusion, the primarily positive associations observed across studies conducted in various locations is further supported by the results from copollutant analyses indicating robust associations, along with evidence from analyses of the C-R relationship. **Collectively,**

this body of evidence is sufficient to conclude that a causal relationship exists between short-term $PM_{2.5}$ exposure and total mortality.

11.2 Long-Term $PM_{2.5}$ Exposure and Total Mortality

The 2009 PM ISA reported that the evidence was "sufficient to conclude that the relationship between long-term $PM_{2.5}$ exposures and mortality is causal" (U.S. EPA, 2009).[79] Two seminal cohort studies, the American Cancer Society (ACS) and the Harvard Six Cities studies provided the strongest evidence for this conclusion (i.e., consistency across studies and among replication and reanalysis of the same cohort; study designs appropriate for causal inference), and were supported by evidence from other cohort studies conducted in North America and Europe. Evidence presented in the 2009 PM ISA was largely consistent with past studies reporting associations between long-term $PM_{2.5}$ exposure and increased risk of human mortality. Additional analyses of the Harvard Six Cities cohort demonstrated a reduction in mortality risk associated with decreases in $PM_{2.5}$ concentrations (Laden et al., 2006). Similarly, Pope et al. (2009) reported that decreases in $PM_{2.5}$ concentrations were associated with increases in life expectancy. Another new line of evidence supporting the causality determination in the 2009 PM ISA was the increased risk in death from cardiovascular disease among a cohort of post-menopausal women with no previous history of cardiovascular disease (Miller et al., 2007).

The following section provides a brief, integrated evaluation of evidence for long-term $PM_{2.5}$ exposure and mortality presented in the previous NAAQS review with evidence that is newly available for this review (see Table 11-5 for study descriptions). This section focuses on assessing the degree to which newly available studies further characterize the relationship between long-term $PM_{2.5}$ exposure and mortality, focusing on studies where long-term average $PM_{2.5}$ concentrations are less than 20 $\mu g/m^3$ across all cities or where at least half of the cities have long-term average $PM_{2.5}$ concentrations less than 20 $\mu g/m^3$ (see Preface). For example, areas of research that inform differences in the exposure window used to evaluate long-term exposures and mortality or comparisons of statistical techniques will be highlighted. Studies that address the variability in the associations observed across $PM_{2.5}$ epidemiologic studies due to exposure error and the use of different exposure assessment techniques will be emphasized. Another important consideration will be characterizing the shape of the concentration-response (C-R) relationship across the full concentration range observed in epidemiologic studies. The evidence in this section will focus on epidemiologic studies because experimental studies of long-term exposure and mortality are generally not conducted. However, this section will draw from the morbidity evidence presented for different health endpoints across the scientific disciplines (i.e., animal toxicological, epidemiologic and controlled human exposure studies) to support the associations observed for cause-specific mortality.

[79] As detailed in the Preface, risk estimates are for a 5 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations, unless otherwise noted.

Table 11-5 North American epidemiologic studies of long-term exposure to $PM_{2.5}$ and mortality.

Study	Study Population	Exposure Assessment	Mean (μg/m³)	Copollutant Examination
Laden et al. (2006) Multicity; U.S. $PM_{2.5}$: 1979–1998 Follow-up: 1979–1998 Cohort Study	Harvard Six Cities Study n = 8,096 white participants enrolled between 1974 and 1977	City-specific averages from monitors (1979–1987); City-specific regression equations based on extinction coefficient and PM_{10} fixed-site monitoring data (1985–1998); r = 0.93	Mean: 10.2–22.0	Correlation (r): NA Copollutant models with: NA
Pope et al. (2009) Multicity, U.S. $PM_{2.5}$: 1979–1983; 1999–2000 Follow-up: 1978–1982; 1997–2001 Cohort Study	American Cancer Society Cancer Prevention Study II n = 383,000 population in study area (1980) n = 482,000 population in study area (2000)	City-specific averages from fixed-site monitors	1979–1983 Mean: 20.61 1999–2000 Mean: 14.10	Correlation (r): NA Copollutant models with: NA
Miller et al. (2007) Multicity, U.S. $PM_{2.5}$: 2000 Follow-up: 1994–2003 Cohort Study	Women's Health Initiative n = 58,610 post-menopausal women; 349,643 person-years of follow-up	City-specific averages from fixed-site monitors within 30 km	Mean: 13.5 90th: 18.3 Range: 3.4–28.3	Correlation (r): NA Copollutant models with: NA
Pope et al. (1995) Multicity, U.S. $PM_{2.5}$: 1979–1983 Follow-up: 1982–1989 Cohort Study	American Cancer Society Cancer Prevention Study II n = 552,138 participants	City-specific averages from fixed-site monitors	Median: 18.2 Range: 9.0–33.5	Correlation (r): NA Copollutant models with: NA
†Pope et al. (2014) Multicity, U.S. $PM_{2.5}$: 1999–2008 Follow-up: 1982–2004 Cohort Study	American Cancer Society Cancer Prevention Study II n = 669,046 participants; 237,201 deaths during 12,662,562 person-years of follow-up	City-specific averages from LUR-BME; cross-validated with 10% of data (R^2 = 0.79); see Beckerman et al. (2013) for details	Mean: 12.6 Range: 1–28	Correlation (r): NA Copollutant models with: NA